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PROSPECTS FOR PRODUCTION OF VACCINES AND OTHER IMMUNIZING AGENTS IN DEVELOPING COUNTRIES

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Preface

This study has been prepared by UNIDO's Division for Industrial Studies, Sectoral Studies Branch, with the aim of drawing attention to the urgent need for a new approach to the problems of production of vaccines and other immunizing agents in developing countries. It will also be used at the Second Consultation on the Pharmaceutical Industry to be held in Budapest from 21 to 25 November 1983.

This area has been studied both for its great potential social benefits for developing countries and because of its inherent possibilities to play a role in an industrialization strategy based on more self-reliance.

The results of the Consultation and subsequent follow-up work will be taken into account, and a revised and up-dated version of the study will be issued in 1984.

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EXPLANATORY NOTES

Prices and market values are given in United States dollars.

A comma (,) is used to distinguish thousands and millions.

A full stop (.) is used to indicate decimals.

A slash between dates (e.g., 1980/81) indicates a financial year.

Use of hyphen between dates (e.g., 1980-2000) indicates the full period involved, including the beginning and end years.

The following forms have been used in tables:

Three dots (...) indicate that data are not available or are not separately reported.

A dash (-) indicates that the amount is nil or negligible.

A blank indicates that the item is not applicable.

Totals may not add up precisely because of rounding.

Besides the common abbreviations, symbols and terms and those accepted by the International System of Units (SI), the following abbreviations have been used in this study.

ECONOMIC AND TECHNICAL ABBREVIATIONS

BCG	Bacillus Calmette-Guérin Vaccine
CBA	Cost-benefit analysis
CPE	Centrally Planned Economy
DPT	Diphtheria and Tetanus Toxoids and Pertussis Vaccine
EPI	Expanded Programme on Immunization
F.D.A.	Food and Drug Administration of the U.S.A.
IU	International unit of potency
Lf	Limes flocculationis, i.e., flocculation unit
PPD	Purified protein derivative
RBA	Risk-benefit analysis

R & D	Research and development
TDR	Special Programme for Research and Training in Tropical Diseases
TPC	Total production costs
U.S.P.	United States Pharmacopeia
US $	United States dollar
UNITAD	Joint UNIDO/UNCTAD model system of world economy

ORGANIZATIONS

IDA	International Dispensary Association
IFPMA	International Federation of Pharmaceutical Manufacturers Association
IMS	International Medical (Marketing) Services
PAHO	Pan American Health Organization
SCRIP	SCRIP World Pharmaceutical News
UNCTAD	United Nations Conference on Trade and Development
UNICEF	United Nations Children's Fund
WHA	World Health Assembly
WHO	World Health Organization

1. INTRODUCTION

Since the beginning of history smallpox has left its mark indelibly stamped upon the medical, policital and cultural efforts of men. Smallpox was already known in India, China and Egypt more than 3,000 years before Christ. Records show severe epidemics in Europe, during the Middle Ages. Introduced into America by the European explorers, it decimated the native population. In the 18th century, smallpox caused between 1,000 to 3,000 deaths annually in London alone. Terror of its presence was constant, such that "no man dared to count his children as his own until after they had had the disease".[1/]

In 1967, when WHO launched its world-wide programme of eradication, there was an estimated 10 to 15 million cases with 2 million deaths annually. The eradication of smallpox had been achieved in 10 years due to the active tracking down of cases and improved use of the vaccine in 33 countries. The last known case was notified on 26 October 1977, in Somalia. In 1982, WHO reported that routine vaccination for smallpox had been discontinued in 150 of the United Nations 158 member states.[2/]

2. BACKGROUND AND JUSTIFICATION

WHO initiated the Expanded Programme on Immunization (EPI) in 1974 and it has become an essential element of the strategy to achieve health for all by the year 2000[3/] with the goal of reducing morbidity and mortality from diphtheria, pertussis, tetanus, measles, poliomyelitis, and tuberculosis by providing immunization against these diseases for every child in the world by 1990.

While the reported numbers of cases and deaths may underestimate the extent of the consequence of those six diseases, and safe and effective vaccines exist for their prevention, they are thought to cause some

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1/ Le Comte de la Condamine, a French mathematician and scientist in the 18th century.

2/ Drug and Cosmetic Industry, 132, October 1982, p.11.

3/ Resolution WHO 30.53 (adopted in May, 1977).

5 million deaths among children under 5 years, while blinding, crippling, or otherwise permanently disabling an additional 5 million.[4/]

The importance of EPI as an essential component of maternal and child health and primary health care was emphasized at various WHO forums.[5/]

The incidence of EPI diseases in developed countries is very low, as a result of compulsory or voluntary vaccination programmes strongly supported and controlled by government authorities.

Some developing countries produce vaccines, but rarely those against childhood diseases.

Up to now, a significant share of the industry's current output in developed countries is exported to developing countries, primarily through UNICEF and PAHO. Many companies have, however, withdrawn from the vaccine field over the last decade.[6/]

The demand for vaccines to prevent childhood diseases is expected to increase, because the present approx. 20% coverage of the target population in developing countries will increase to 100% if the EPI succeeds and world population trends indicate an increase of the target population itself. Both of these factors will primarily affect demand in developing countries.

Other factors also deserve analysis. For example, some vaccines intended mainly for special target populations - influenza, hepatitis B, human diploid-cell rabies, etc. vaccines - have a limited availability in developing countries at a prohibitive price for the great majority of the population.

4/ Sixth Report on the World Health Situation, Part I: Global analysis, p.93 (1980).

5/ Resolution WHA 31.53 (adopted in May 1978); Declaration of Alma Ata, September 1978.

6/ IFPMA Position Paper on the Vaccines and Sera Industry, October 1981.

Industrial research and development of new vaccines for the prevention and treatment of diseases, prevailing in developing countries and for which no satisfactory or only palliative therapy exists, are handicapped by the lack of funds and know-how.

Developing countries are contemplating vaccine production also to save hard currency and for reasons of self-reliance in this very important field of public health.

It is reasonable to assume that the particularly good international co-operation in this field is going to continue also in the future both in the identification of problems and in their solution.

In light of the importance of all previously described subjects and with a view of assisting the developing countries in the establishment and/or expansion of their pharmaceutical industry, UNIDO has decided to study the current situation and future scenarios of some aspects of the local production of immunizing agents and diagnostic antigens in developing countries.

3. OBJECTIVES OF THE STUDY

The overall objective is to help developing countries achieving the goal of "Health for all by the year 2000" as defined by the WHO.

The industrial objective is (a) to assist developing countries to establish and/or to expand local production of biological preparations through the identification and analysis of the current economic and technical constraints delaying industrial development, and (b) to propose solutions to reduce the effect of such constraints.

4. COST-BENEFIT AND RISK-BENEFIT ANALYSIS OF IMMUNIZATION PROGRAMMES

Social cost-benefit analysis (CBA) has become an internationally applied method for the appraisal of public sector investments.

The principal components of costs of preventive vaccination are:[7]

- wages of immunizing and professional staff,
- travel costs,
- cost of vaccines, and
- immunity tests.

WHO estimates a global average unit cost --cost per fully immunized infant--of approximately US$ 3.00.[8]

The main categories of benefits include:

- averted treatments costs,
- avoided production loss as a result of illness,
- avoided production loss as a result of premature death,
- improved health,
- positive external effects.

Although it is difficult to measure some of these benefits quantitatively, studies on vaccination against infectious diseases are used as textbook examples of positive outcomes of CBA, since under certain epidemiological conditions people may be willing to pay for others receiving vaccination. This factor might have played a role in the eradication of smallpox and can favourably affect international co-operation in the implementation of the EPI.

The methodologies and findings of some 20 economic evaluations of immunization programmes have recently been reviewed.[9]

7/ B. Jönsson: Cost-benefit analysis in public health and medical care, Printab, Lund, 1976.

8/ A.L. Creese and R.H. Henderson: Cost-benefit analysis and immunization programmes in developing countries. Bulletin of the WHO, 58 (3): 491-497 (1980).

9/ IFPMA Document SV 67: Cost effectiveness and cost benefit analysis of immunization programmes in developing countries. September, 1982.

As long as the incidence of a disease is very high, the effects on its victims are severe, and there is no effective treatment, vaccination generates social benefits exceeding its costs. If the incidence of an infectious disease becomes low and the risk of an imported epidemic is minimum, vaccination policy will be based on risk-benefit analysis (RBA). For example, general vaccination against smallpox was discontinued in the U.S.A. already in 1971, because it was found that more people died of smallpox vaccination than of smallpox and there was also a relatively high incidence of neurological and dermatological side effects against no case of smallpox.

The difference between the morbidity and mortality patterns explains that in developing countries CBA, while in industrialized countries also RBA is used in the social and economic evaluation of vaccination programmes. It should be mentioned in this context, that the risks of vaccination are closely related to the adverse reactions, which in turn depend on the purity (quality) and type (e.g., human tetanus immune globulin versus equine or bovine antitoxin) of the biological product employed. In this study, good quality is considered a pre-requisite for CBA or RBA and is defined as a product that complies with the WHO requirements for biologicals. If a biological product is not included in the WHO Revised Model List of Essential Drugs 1983, the U.S.P. or F.D.A. requirements are taken for standard.

Since social benefits outweigh social costs and international benefits are enjoyed by many countries, direct involvement of health authorities in programme implementation is a pre-requisite and participation of public sector in the production is desirable in order to promote the idea by political means that primary health care should be provided according to the need and not according to the propensity to purchase.

5. DEFINITION AND CLASSIFICATION OF BIOLOGICALS

Biologicals have been defined, for example, as (a) a product of biological origin, which cannot be controlled chemically or physically,[10/] or (b) a

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10/ IMS Pharmaceutical Marketletter, 13 Dec. 1982, p. 9.

product obtained directly from, or that has been derived from, living matter-- animals, plants, or microorganisms. In this study, "Biological product means any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment, or cure of diseases or injuries of man"-- a definition employed by the Bureau of Biologics of the Food and Drug Administration (FDA) of the U.S.A.[11/]

Classification of Biological Products[12/]

For Active Immunization:
Bacterial Vaccines
Bacterial Antigens
Multiple Antigen Preparations
Viral and Rickettsial Vaccines
Toxoids

For Passive Immunization:
Antitoxins
Antivenoms
Immune Globulins

Diagnostic Agents
Toxins
Tuberculin
Virus Antigens
Proteins

Human Blood Derivatives:
Whole blood
Rh_o(D) Immune Globulin
Plasma
Radioiodinated Serum Albumin
Normal and Immune Serums
Packed Red Cells
Grouping Serums
Anti-Rh Typing Serums

Allergens
Allergenic Extracts
Proteins

Miscellaneous
Venoms, Pyrogens

The WHO Revised Model List of Essential Drugs 1983 contains 21 biological products (Annex 1), of which the following 4 items have been selected as priority drugs and sample population for more detailed analysis in this study to illustrate some global aspects of the trade and production.

Name of product	Abbreviation
1. BCG Vaccine (dried)	BCG
2. Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed	DPT
3. Measles Virus Vaccine Live	Measles
4. Poliomyelitis Vaccine (oral, live attenuated)	Polio

11/ Remington's Pharmaceutical Sciences, 16th ed., Mack Publishing Co. (1980), p. 1324.

12/ ibid, p. 1327.

Other biologicals will be also used examples to illustrate the importance of the related hypothesis or argument.

6. BRIEF DESCRIPTION OF THE BIOLOGICAL INDUSTRY SUB-SECTOR

The Biological Sub-Sector is quite different from other sub-sectors of the pharmaceutical industry as far as manufacturing and processing methods are concerned, although there are a few unit operations, e.g., fermentation, or filling of suspensions into ampoules, which are similar. The organization of the production has very special aspects, e.g., tetanus premises must be isolated from other production units and capacity of equipment is not convertible; human blood derivatives should be produced separately from other biologicals, etc. Hence, an enterprise producing biologicals is usually a separate company or separate division of a large company. It is worth mentioning that government involvement in this sub-sector is higher than in other branches of the pharmaceutical industry.

7. PRICE ANALYSIS

Price trends have been analysed to estimate the value of production in 1980, 1990 and 2000. Table I shows historical prices for selected biologicals.

Table I: Past single dose prices of EPI vaccines[13/]

(dollars)

Product	Unit pack	79/80	80/81	81	82
DPT	10 doses	0.038	0.041	0.041	0.034
Oral polio	10 doses	0.022	0.025	0.035	0.030
Measles	10 doses	0.140	0.099	0.106	0.128
BCG	20 doses	0.055	0.059	0.054	0.049

13/ PAHO CSP 21/18 of 19 July 1982, p.2.

Three points deserve comments:

(a) prices in Table I are very competitive since they reflect the outcome of international tenders;

(b) with the exception of measles, all other prices show a decreasing tendency between 1981 and 1982;

(c) the appreciation of US$ in 1982 contributed to the reduction of prices in that year.

It should also be mentioned that domestic market prices are much higher in most countries.

Possible future prices are shown in Table II. Figures have been calculated on the basis of 1982 PAHO prices and assuming a 4% annual growth rate:

Table II: Projected single dose prices for EPI vaccines

(current dollars)

Product	1982	1985	1990	1995	2000
DPT	0.034	0.038	0.047	0.057	0.069
Oral polio	0.030	0.034	0.041	0.050	0.060
Measles	0.128	0.144	0.175	0.213	0.259
BCG	0.049	0.055	0.067	0.082	0.099

8. PRESENT AND PROJECTED DEMAND 1990 AND 2000 FOR IMMUNIZING AGENTS

8.1 Demand Determinants

Apart from the economic and medical resources which must be available for the purchase and distribution of immunizing agents and diagnostic antigens, there are many other factors that influence the demand, such as:

- compulsory vaccination programmes,
- availability of vaccines free of charge,
- special target populations,
- epidemics,
- natural catastrophes,
- war,
- government promotion,
- industry promotion,
- new dosage forms,
- alternative therapies,
- alternative preventive measures,
- alternative diagnostic methods,
- high antibody titer in target population, and
- others.

Some product-specific demand determinants are also mentioned, as illustrative examples.

BCG vaccine. The greatest number of tuberculous infections are observed during the first 5 years of life and at very old age.[14/] Efficient therapy exists. Hence, target population consists mainly of neonates.

Tetanus toxoid alone, or as a component of DPT. Tetanus is accidental in origin and not contagious. All human beings are exposed to risk throughout their lives. The illness itself does not immunize. Tetanus toxoid is very effective, very safe and cost effective. Fatality rate is high and satisfactory therapy does not exist. Neonatal tetanus accounts for 20 to 50 per cent of the total infant mortality in many areas and immunization of pregnant women would prevent about one million infant deaths per year on the global level, primarily in developing regions.[15/]

14/ Editorial. BCG vaccination after the Madras study. Lancet, (London), 2:309, 1981.

15/ Weekly Epidemiological Record (WHO), 58:3:13-18, 1983.

Pertussis vaccine. Sensationalized medical accounts of vaccine side-effects have frightened parents of pertussis vaccination. The statistical data show that in the United Kingdom the estimated attributable risk of serious neurological disorders occurring within 7 days after immunization with DPT in previously normal children, irrespective of outcome, is 1 in 110,000 injections. The rate for previously normal children with neurological disorders persisting one year later is 1 in 310,000.[16] On the other hand, when pertussis vaccination coverage reaches at least 90 per cent, pertussis virtually disappears from the population.[17]

Poliomyelitis vaccine live, oral. Convenience of administration and excellent efficiency in industrialized countries favour application of the oral vaccine. However, oral poliomyelitis vaccine has been found less effective in tropical countries and application of the inactivated vaccine or combined use of the two, is under consideration.[18]

The above examples illustrate that there are differences in the evaluation of the benefits, risks and cost-effectiveness of vaccines. This is probably the main reason why a generally accepted, standard vaccination programme does not exist.

8.2 Methodology of Demand Estimation

The method, used to calculate an order of magnitude estimate of the vaccine demand for the prevention of the six childhood diseases, is described in Annex 2.

An important factor affecting principally future demand for vaccines is the eradicability of a disease. Figure 1 shows the projected life-cycle curve of measles based on the assumption that the disease will be eradicated by the year 2000.

16/ Koplan, J.F. et al: Pertussis vaccine - analysis of benefits, risks and costs. New England Journal of Medicine (Boston, U.S.A.), 30:906-911. 1979.

17/ Weekly Epidemiological Record (WHO), 56:19:150-151, 1981.

18/ Assaad, F.: Reassessment of the place if inactivated poliomyelitis vaccine in national immunization programmes. Development in Biological Standardization (Basel), 47:275-282, 1981.

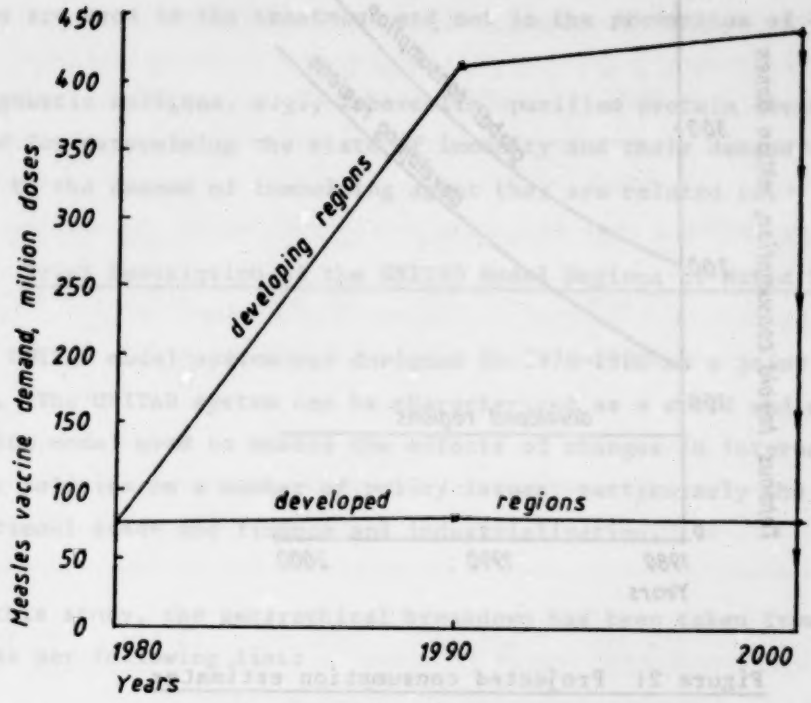

Figure 1: Estimated demand curve for measles, given eradication by the year 2000

The demand for such type vaccines is temporary, regardless of how long the period is, and becomes nil by the time the disease is eradicated.

Eradicability deserves special attention when planning new investment projects, because the demand for vaccines used for the prevention of eradicable diseases is reduced to nil soon after the necessary health resources are made available. An example to support this statement is the successful smallpox eradication campaign.

The demand for vaccines against infectious diseases that cannot be eradicated is illustrated through the projected demand curve of tetanus toxoid based on the assumption that only newborns require a starter dose and only pregnant women in developing countries are given a starter and a booster dose.

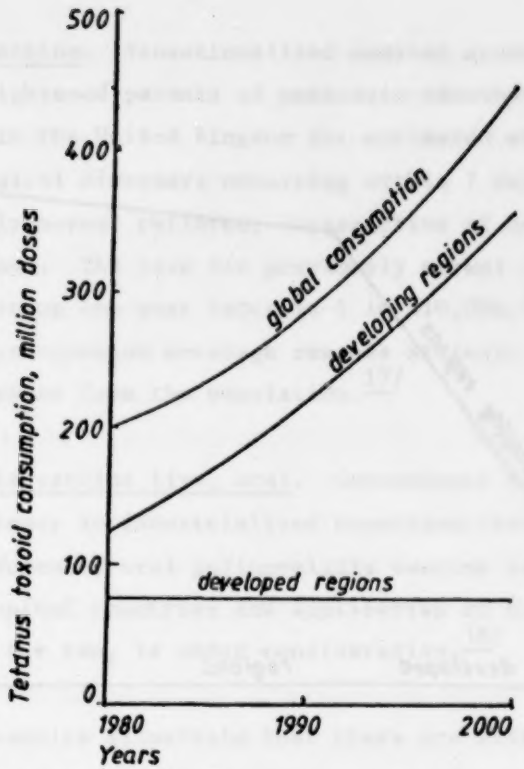

Figure 2: Projected consumption estimates for tetanus toxoid (1980-2000)

The maintenance "demand" for such type of vaccines is permanent and is characterized by a simplified formula:

$$D = c \left[(C_{Bt} + B_t) (1 + w) \right]$$

and changes in proportion to the birth rate. Hence, planning new investment projects is fully justified for the production of such vaccines on the basis of this criterion.

The demand for other immunizing agents for active immunization, e.g., Diphtheria and Tetanus toxoids, or Influenza Virus vaccine, Meningococcal vaccine, Rabies vaccine, Typhoid vaccine, Yellow Fever vaccine follow usually the demand pattern of diseases which cannot be eradicated. Sometimes the continuity of the trend is broken by unexpected peaks, for instance, in case of rabies due to epidemics among wild animals.

The demand for immunizing agents for passive immunization, e.g., Anti-D immunoglobulin, Antirabies hyperimmune serum, Antivenom sera, Diphtheria antitoxins should be studied in analogy to drugs, since these biological products are used in the treatment and not in the prevention of diseases.

Diagnostic antigens, e.g., Tuberculin, purified protein derivative (PPD), are used for determining the state of immunity and their demand is closely related to the demand of immunizing agent they are related to.

8.3 Brief Description of the UNITAD Model Regions of World Economy

The UNITAD model system was designed in 1979-1980 as a joint UNIDO/UNCTAD project. The UNITAD system can be characterized as a world and economy-wide simulation model used to assess the effects of changes in international and domestic policies on a number of policy issues, particularly the problems of international trade and finance and industrialization.

In this study, the geographical breakdown has been taken from the UNITAD model, as per following list:

Developed regions

1. North America
2. Western Europe
3. Centrally Planned Economies (CPE), Europe
4. Japan
5. Other developed

Developing regions

6. Latin America
7. Africa, South of the Sahara (Tropical Africa)
8. North Africa and West Asia (West Asia)
9. Indian Subcontinent (South Asia)
10. East and South-East Asia (East Asia)
11. CPE, Asia

Demographic country data relevant to this study are given in Annexes 3 and 4. The regional demographic data are shown in Table III.

Table III: Annual mid-year population and number of births medium variant, 1980, 1990 and 2000 by UNITAD regions

UNITAD Regions	Population (in 1000) 1980	1990	2000	Births (in 1000) 1980	1990	2000
1. North America	247 717	273 650	295 328	3 947	4 453	4 219
2. Western Europe	420 384	442 024	462 629	6 530	6 813	6 692
3. CPE Europe	378 249	409 782	435 482	6 714	6 996	6 799
4. Japan	116 551	123 185	129 282	1 722	1 486	1 749
5. Other developed countries	47 041	58 838	73 139	1 329	1 647	1 938
DEVELOPED REGIONS	1 209 942	1 307 479	1 395 860	20 242	21 395	21 397
6. Latin America	358 229	452 449	558 050	11 406	13 194	14 470
7. South-Sahara Africa	330 891	450 878	614 259	14 783	19 475	24 236
8. North Africa Middle East	195 108	262 564	341 982	7 924	9 657	10 798
9. South Asia	941 151	1 153 436	1 376 194	33 387	35 369	35 851
10. South-East Asia	308 110	370 773	432 323	9 512	9 802	9 466
11. CPE Asia	1 078 682	1 231 858	1 382 472	23 533	23 966	24 366
DEVELOPING REGIONS	3 212 171	3 921 958	4 705 280	100 545	111 463	119 187
UNITAD TOTAL	4 422 113	5 229 437	6 101 140	120 787	132 858	140 584
WORLD TOTAL	4 432 147	5 241 911	6 115 514	121 067	133 182	140 905

Source: Annex 3 and Annex 4

8.4 Methodological Assumptions

The following simplified assumptions have been made in the estimates:

(1) the number of births equals to the number of children surviving to vaccination age,

(2) the number of pregnant women equals to the number of births, and

(3) the demand is directly proportional to the size of target population.

Consumption estimates 1980, and projections 1990 and 2000 were calculated by using the simplified formula given in page 12. B_t values were taken from Table III. C_{Bt} was used only to calculate tetanus toxoid demand for pregnant women in developing countries, with one starter and one booster dose, i.e., $C_{Bt} = 2B_t$.

The target population coverage values for the high-series (a), medium-series (b) and low-series (c) estimates and projections are summarized in Table V.

Table IV: Coverage estimates of target populations for EPI vaccination by UNITAD major regions (percentage)

Major region	DPT (a)	DPT (b)	DPT (c)	Polio (a)	Polio (b)	Polio (c)	Measles (a)	Measles (b)	Measles (c)	BCG (a)	BCG (b)	BCG (c)
1980												
UNITAD 1 - 5	100	95	90	100	95	90	100	95	90	60	50	40
UNITAD 6 - 11	21	18	15	21	18	15	30	27	24	35	31	27
1990												
UNITAD 1 - 5	100	95	90	100	95	90	100	95	90	55	45	35
UNITAD 6 - 11	40	30	20	90	30	20	90	40	30	55	45	35
2000												
UNITAD 1 - 5	100	95	90	-	95	90	-	95	90	50	40	30
UNITAD 6 - 11	50	40	30	-	40	30	-	50	40	70	60	50

The high-series projection is based on the assumption that EPI goals will be achieved, hence only newborns will be vaccinated against the 6 EPI diseases and special target populations against tetanus from 1990 onwards. A high coverage (90 per cent) was chosen for measles and poliomyelitis in 1990, because this was considered a pre-requisite for eradication of the diseases by the year 2000.

The medium-series consumption estimates 1980 for the developing regions were calculated with reported data for Africa.[19/]

Low-series estimates and all projections, except measles and poliomyelitis optimistic scenarios, have been calculated with arbitrarily chosen coverage values.

BCG demand has been assumed to decrease moderately in the developed regions.

The results of the calculations are summarized in Tables V, VI, VII and VIII.

19/ WHO EPI/GEN/82/6: Report of the Expanded Programme on Immunization, Global Advisory Group Meeting, 18-22 October 1982, Brazzaville, p.7.

Table V: Estimated global consumption 1980
of EPI vaccines by UNITAD regions
(million doses)

Major regions	DPT / Polio			Measles			BCG		
	(a)	(b)	(c)	(a)	(b)	(c)	(a)	(b)	(c)
UNITAD 1	14.8	14.1	13.3	4.9	4.7	4.4	3.0	2.5	2.0
2	24.5	23.3	22.0	8.2	7.8	7.3	4.9	4.1	3.3
3	25.2	23.9	22.7	8.4	8.0	7.6	5.0	4.2	3.4
4	6.5	6.1	5.8	2.2	2.0	1.9	1.3	1.1	0.9
5	5.0	4.7	4.5	1.7	1.6	1.5	1.0	0.8	0.7
Developed regions:	75.9	72.1	68.3	25.3	24.0	22.8	15.2	12.7	10.1
UNITAD 6	9.0	7.7	6.4	4.3	3.8	3.4	5.0	4.4	3.8
7	11.6	10.0	8.3	5.5	5.0	4.4	6.5	5.8	5.0
8	6.2	5.3	4.5	3.0	2.7	2.4	3.5	3.1	2.7
9	26.3	22.5	18.8	12.5	11.3	10.0	14.6	13.0	11.3
10	7.5	6.4	5.4	3.6	3.2	2.9	4.2	3.7	3.2
11	18.5	15.9	13.2	8.8	7.9	7.1	10.3	9.2	7.9
Developing regions:	79.2	67.9	56.6	37.7	33.9	30.2	44.0	39.2	33.9
UNITAD WORLD : TOTAL	155.1	140.0	124.9	63.0	57.9	53.0	59.2	51.9	44.0

Notes: (i) The above figures are best estimates and should be used with care.
(ii) The additional demand for tetanus toxoid to pregnant women in developing regions is estimated at (a) 52.8, (b) 45.3, and (c) 37.7 million doses, respectively.

Table VI: Projected global consumption 1990 of EPI vaccines by UNITAD regions (million doses)

Major regions	DPT (a)	DPT (b)	DPT (c)	Polio (a)	Polio (b)	Polio (c)	Measles (a)	Measles (b)	Measles (c)	BCG (a)	BCG (b)	BCG (c)
UNITAD 1	16.7	15.9	15.0	16.7	15.9	15.0	5.6	5.3	5.0	3.1	2.5	1.9
2	25.5	24.3	23.0	25.5	24.3	23.0	8.5	8.1	7.7	4.7	3.8	3.0
3	26.2	24.9	23.6	26.2	24.9	23.6	8.7	8.3	7.9	4.8	3.9	3.1
4	5.6	5.3	5.0	5.6	5.3	5.0	1.9	1.8	1.7	1.0	0.8	0.7
5	6.2	5.9	5.6	6.2	5.9	5.6	2.1	2.0	1.9	1.1	0.9	0.7
Developed regions:	80.2	76.2	72.2	80.2	76.2	72.2	26.7	25.4	24.1	14.7	12.0	9.4
UNITAD 6	19.8	14.8	9.2	44.5	14.8	9.2	14.8	6.6	4.9	9.1	7.4	5.8
7	29.2	21.9	13.6	65.7	21.9	13.6	21.9	9.7	7.3	13.4	11.0	8.5
8	14.5	10.9	6.8	32.6	10.9	6.8	10.9	4.8	3.6	6.6	5.4	4.2
9	53.1	39.8	24.8	119.4	39.8	24.8	39.8	17.7	13.3	24.3	19.9	15.5
10	14.7	11.0	6.9	33.1	11.0	6.9	11.0	4.9	3.8	6.7	5.5	4.3
11	35.9	27.0	16.8	80.9	17.0	16.8	27.0	12.0	9.0	16.5	13.5	10.5
Developing regions:	167.2	125.4	78.0	376.2	125.4	78.0	125.4	55.7	41.8	76.6	62.7	48.8
UNITAD WORLD : TOTAL	247.4	201.6	150.2	456.4	201.6	150.2	152.1	81.1	65.9	91.3	74.7	58.2

Note: the additional demand for tetanus toxoid to pregnant women in developing regions is projected at (a) 111.5, (b) 83.6, and (c) 52.0 million doses, respectively.

Table VII: Projected global consumption 2000 of EPI vaccines by UNITAD regions (million doses)

Major regions	DPT (a)	DPT (b)	DPT (c)	Polio (a)	Polio (b)	Polio (c)	Measles (a)	Measles (b)	Measles (c)	BCG (a)	BCG (b)	BCG (c)
UNITAD 1	15.8	15.0	14.2	-	15.0	14.2	-	5.0	4.7	2.6	2.1	1.6
2	25.1	23.8	22.6	-	23.8	22.6	-	7.9	7.5	4.2	3.3	2.5
3	25.5	24.2	22.9	-	24.2	22.9	-	8.1	7.6	4.2	3.4	2.5
4	6.6	6.2	5.9	-	6.2	5.9	-	2.1	2.0	1.1	0.9	0.7
5	7.3	6.9	6.5	-	6.9	6.5	-	2.3	2.2	1.2	1.0	0.7
Developed regions:	80.2	76.2	72.2	-	76.2	72.2	-	25.4	24.1	13.4	10.7	8.0
UNITAD 6	27.1	21.7	16.3	-	21.7	16.3	-	9.0	7.2	12.7	10.9	9.0
7	45.4	36.4	27.3	-	36.4	27.3	-	15.1	12.1	21.2	18.2	15.1
8	20.2	16.2	12.1	-	16.2	12.1	-	6.7	5.4	9.4	8.1	6.7
9	67.2	53.8	40.3	-	53.8	40.3	-	22.4	17.9	31.4	26.9	22.4
10	17.7	14.2	10.6	-	14.2	10.6	-	5.9	4.7	8.3	7.1	5.9
11	45.7	36.5	27.4	-	36.5	27.4	-	15.2	12.2	21.3	18.3	15.2
Developing regions:	223.5	178.8	134.1	-	178.8	134.1	-	74.5	59.6	104.3	89.4	74.5
UNITAD WORLD : TOTAL	303.7	255.0	206.3	-	255.0	206.3	-	99.9	83.7	117.7	100.1	82.5

Note: The additional demand for tetanus toxoid to pregnant women in developing countries is projected at (a) 149.0, (b) 119.2, and (c) 89.4 million doses respectively.

Eradication of poliomyelities and measles has been assumed in the high-series projection, hence demand in 2000 is nil.

Table VIII: Comparison of 1980 consumption estimates with 1990 and 2000 medium-series demand projections for EPI vaccines (million doses)

Product	1980	1990	2000
DPT			
UNITAD 1 - 5	72.1	76.2	76.2
UNITAD 6 - 11	67.9	125.4	178.8
WORLD TOTAL	140.0	201.6	255.0
Polio			
UNITAD 1 - 5	72.1	76.2	76.2
UNITAD 6 - 11	67.9	125.4	178.8
WORLD TOTAL	140.0	201.6	255.0
Measles			
UNITAD 1 - 5	24.0	25.4	25.4
UNITAD 6 - 11	33.9	55.7	74.5
WORLD TOTAL	57.9	81.1	99.9
BCG			
UNITAD 1 - 5	12.7	12.0	10.7
UNITAD 6 - 11	39.2	62.7	89.4
WORLD TOTAL	51.9	74.7	100.1
Tetanus			
UNITAD 1 - 5	...	...	...
UNITAD 6 - 11	45.3	83.6	119.2
WORLD TOTAL	45.3	83.6	119.2

Note: Except pregnant women, other special target populations for tetanus toxoid inoculation have been neglected in all regions.

8.5 Analysis of Demand Estimates 1980 and Projections 1990 and 2000 for EPI Vaccines

Unless otherwise stated, analysis refers to medium-series estimates and projections.

Demand estimates 1980

Estimates in Table V show that 48.5 per cent of the industry's estimated global output for DPT and poliomyelitis vaccines was consumed in the developing regions. The same values for measles and BCG vaccines are 58.5 per cent and 75.5 per cent, respectively.

DPT and Poliomyelitis vaccine consumption estimates should be regarded as conservative figures, because incomplete vaccinations (namely, children that have received only one or two doses) are not accounted for. This factor affects present demand considerably and might increase consumption in developing regions to a 6 times higher value than that shown in Table V. The relatively higher consumption values for Measles and BCG vaccines in developing regions can be attributed to the simpler implementation (single inoculation) of the vaccination programme.

Calculated with reference to 1980/81 PAHO single dose prices, the global sales value of the production was US$ 5.7 million for DPT, US$ 2.6 million for oral polio, US$ 5.7 million for measles and US$ 3.1 million for BCG vaccine, respectively. These figures are strong underestimates of the market value. In 1980, for example, a single dose of DPT was sold for US$ 0.065 by a non-profit procurement organization supplying developing countries,[20/] for US$ 0.187 in the U.S.A.[21/] and for US$ 0.184 in Austria.[22/] According to other sources, the costs for oral polio vaccine were US$ 5.00 and for DPT US$ 1.82 in the U.S.A. in 1982.[23/] Assuming a 100 per cent margin between

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20/ IDA Price Indicator, November 1980, p.4.

21/ Red Book (U.S.A.) 1980, p. 464.

22/ Spezialitätenpreisliste, Dezember 1980, p. 54.

23/ Drug and Cosmetic Industry, Sep. 1982, p. 10.

consumer's prices and ex-factory prices, these figures would be US$ 0.83 for a single dose of Polio vaccine and US$ 0.30 for a single dose of DPT. It should be mentioned in this context that domestic prices might include the costs of national government quality control, while this component is not included in the export price. As evidenced by the above figures, market prices are higher than international tender prices and domestic prices are higher than export prices. This means, in turn, that the true global sales values of the production are several times higher than those calculated with PAHO 1980 single dose prices and there could be a great variation of prices for individual products and among different countries.

The demand for the only diagnostic agent related to the EPI, Tuberculin, purified protein derivative (PPD), has been neglected in this study, because the vaccination programme used for demand calculation does not make provision for BCG boosters. For informative purpose, the PPD demand in the developed regions could be taken equal to the BCG demand.

Demand Projections 1990 and 2000

The figures of Tables VI and VII have been rearranged for convenience in Table VIII, from which it can be seen that the demand increases moderately in the developed regions for DPT, Poliomyelitis and Measles vaccines, whereas the BCG demand decreases due to the assumed decreasing target population coverage.

On the other hand, the demand is approx. doubled by 1990 and increases further till 2000 in the developing regions. Hence, nearly all the increase in demand is expected in the developing regions. Calculated with reference to projected single dose prices (Table II), the global sales value of the production would be, as follows:

Table IX: Global sales value estimates 1980, 1990 and 2000 for EPI Vaccines ($ million current prices)

Product	1980	1990	2000
DPT	5.7	9.5	17.6
Oral polio	3.5	8.3	15.3
Measles	5.7	14.2	25.9
BCG	3.1	5.0	9.9
WORLD TOTAL	18.0	37.0	68.7

These figures should be considered as cautious estimates, since the lowest actual and the minimum-expected projected single dose prices were used in the calculation. On the other hand, the medium-series consumption projections seem to be realistic both on political and marketing considerations.

All scenarios show that the importance of the developing regions in the global market is continuously increasing. The current US$ market share of developing regions will increase from the 56.1 per cent in 1980 to 67.8 per cent in 1990 and 74.4 per cent in 2000. The life-cycle curves for the individual products have reached the saturation point in the developed regions, while they are still in the exponential stage in the developing regions.

Potential additional demand 1990

There is a single-time demand for launching an eradication and prevention campaign for EPI diseases on the global level in 1990, when the target population could include the whole but preferably not less than 90 per cent of the total population in the developing regions. The simplified formula given in page 12 can be used to calculate such a demand. The suggested variables are shown in Table X.

Table X: Possible immunization schedule for EPI vaccination programme 1990

Disease	C_{St}	C_{Bt}	B_t	w
Diphtheria	-	-	-	0.25
Pertussis	-	-	-	0.25
Tetanus	1 dose	1 dose	-	0.25
Measles	1 dose	-	-	0.25
Poliomyelitis	1 dose	2 doses	-	0.25
Tuberculosis	1 dose	-	-	0.25

If the coverage of the target population for DPT, Poliomyelitis, Measles and BCG vaccines is taken for 20, 20, 30 and 35 per cent, respectively, then the additional vaccine demand could be calculated for the 70, 70, 60 and 55 per cent of the annual mid-year population 1990, taking into account that diphtheria and pertussis should not be given to adults. The results are shown in Table XI.

Table XI: Estimated additional demand 1990 for EPI vaccines including total population in developing countries in the starting programme (million doses)

Major regions		Tetanus	Polio	Measles	BCG
UNITAD	6	791.8	1 187.7	339.3	311.1
	7	789.0	1 183.6	338.2	310.0
	8	459.5	689.2	196.9	180.5
	9	2 018.5	3 027.8	865.1	793.0
	10	648.9	973.3	278.1	254.9
	11	2 155.8	3 233.6	923.9	846.9
Developing regions:		6 863.4	10 295.1	2 941.5	2 696.3
1990 high-series projection		278.7	376.2	125.4	76.6
UNITAD WORLD TOTAL:		7 142.1	10 671.3	3 066.9	2 772.9

Calculated with projected single dose prices, the overall global sales value, including high series projected demands, would be US$ 438 million for oral polio, US$ 537 million for measles, US$ 286 million for tetanus toxoid (US$ 0.04 per single dose) and US$ 186 million for BCG vaccine. These figures might be reduced, if certain age groups are not considered susceptible to infection due to natural or acquired immunity. Nevertheless, the additional demand estimates could be regarded as indicators of the cost component of vaccines, at very competitive prices, if the total population in developing regions were included in the launching of a world-wide campaign.

If the susceptible part of the total population is not vaccinated in an organized way, the incidence of the diseases will become relatively higher in the older age-groups and eradication of a disease will last longer.

An interesting aspect of this problem is the industrial challenge to supply vaccines in 23 to 35 times in excess of the usual demand in 1990.

Since the EPI is focused on newborns and pregnant women, this aspect is disregarded at this stage.

8.6 Demand for Other Immunizing Agents

Immunizing agents identified as essential drugs by the WHO allow sometimes for choice between alternatives for the same biological products.

Rabies vaccine is one of these cases. Rabies vaccine of duck-embryo origin is generally used. Human diploid cell strain vaccine against rabies was developed in the early 1970s. The human diploid cell strain is patented and the number of vaccine suppliers is limited. The vaccine component of the treatment with the duck-embryo vaccine costs approximately US$ 12.30 as against approximately US$ 140.60 for human diploid cell strain vaccine.[24/] The latter produces a higher antibody titer, and some persons show a serious allergy to duck embryo vaccine.

24/ IDA Price Indicator, January 1983.

In spite of the apparent medical advantages of the human diploid cell strain vaccine, the demand will probably continue for the duck embryo vaccine, at least in developing regions, until treatment costs with the human diploid cell vaccine become competitive.

Hepatitis B Vaccine

Hepatitis B virus is responsible for 100,000 to 200,000 cases of hepatitis each year in the United States, with nearly 2,000 fatalities. Among survivors, chronic infection is a serious long-term complication which occurs in 5 to 10 per cent of the cases and may lead to liver cirrhosis and primary liver cancer.25/

About 80% of liver cancer occur as a result of infection with hepatitis B virus.

A total of three doses of Hepatitis B vaccine offers virtually complete protection against hepatitis B, but not hepatitis A or non-A: non-B. The three dose treatment costs approx. US$ 100.26/

An estimated 250,000 develop liver cancer each year in the Third World countries alone and researchers believe that vaccination could save 200,000 lives a year.27/

Hepatitis B vaccine is not available in developing countries or in many industrialized countries either, and this situation is not expected to change by 1990 or 2000 because of the donor (human hepatitis B virus carriers) problem and the high-level technology involved in the production.

25/ FDA Summary for Basis of Approval, BOB Reference, No. 9-240, p.3

26/ Drug Topics, August 16, 1982,p. 23.

27/ SCRIP No. 802, 13 June 1983, p.23.

Calculating with the above data, the market value for a target population of 100,000 patients would be US$ 10 million, i.e., approx. 56 per cent of the total global value of the market for EPI vaccines in 1980.

Tetanus antitoxin is indicated in the WHO Revised Model List of Essential Drugs mainly for passive immunization against tetanus after deep, penetrating and dirty wounds. Due to the limited availability of the starting material for manufacture (blood serum or plasma of healthy horses that have been immunized against tetanus toxoid and toxin), treatment cost with tetanus antitoxin are relatively expensive. The preferred alternative treatment with human Tetanus Immune Globuline --longer protection, freedom from undesired effects, and only one-tenth the dosage compared to antitoxin of animal origin-- is even more expensive and the product should be locally manufactured, since collection of the blood plasma from adult human donors, who have been immunized with tetanus toxoid, needs special organization and exports is restricted on ethical grounds.

The use of immunizing agents derived from animal sera can be avoided almost entirely with the proper use of vaccines and toxoids. An exception is antirabies hyperimmune serum of equine origin and certain other lifesaving antitoxins, such as Antivenom (snakebite) sera.

8.7 Conclusion of Demand Analysis and Projection

Developing countries as a group constitute an important market for EPI vaccines. A significant share of the present consumption is supplied through UNICEF and PAHO free of charge or at very favourable prices.

There is also a demand for other immunizing agents in developing countries, some of which are lifesaving, whereas others might be needed to prevent serious epidemics.

Medical considerations would justify the need for improved vaccines (such as human diploid cell rabies vaccine) as well as for new vaccines (Hepatitis B vaccine), but these are scarcely available in developing countries, or not at all, due to both financial and technological constraints.

The 1990 and 2000 demand projections indicate that all the increase in EPI vaccine demand is expected in the developing regions. Demand for measles and poliomyelitis vaccine, however, might reduce to nil if and when the diseases are eradicated.

The demand for other immunizing agents is also likely to increase, but economic and technological constraints will limit market growth well below the need in developing countries.

9. SUPPLY OF IMMUNIZING AGENTS

A significant number of companies has recently withdrawn completely or partially from the vaccine field in industrialized countries. Vaccines included in the EPI are more affected than others. For example, 15 years ago in the USA there were six producers of live measles virus vaccine, whereas today there is only one. Three of the seven manufacturers licenced to produce DPT vaccine are still on the market, and one of the three licenced to manufacture oral polio vaccine has chosen to leave that market. A 1977 American study suggests that "relatively low profit margin, high production risks, increasing R and D costs, difficulties in clinical testing, and increasingly stringent governmental standards of safety and efficacy all are formidable constraints to private investment".28/

Nevertheless, the supply position is satisfactory and there is keen price competition amongst the bidders of international tenders. This can probably be attributed partly to the obligation to supply the domestic market, and partly to the low utilization of existing capacities.

The purchases of UNICEF, PAHO and other donors constitute a significant share of the global demand, for example, in case of measles:

28/ Drug and Comestic Industry, Sep. 1982, p.10.

Budget year	million doses
1978/79	13.6
1979/80	8.9
1980/81	8.0
1982/83	9.0

which represents approximately 14 to 24 per cent of the estimated global demand in 1980.

On the other hand, it causes concern that not all producers are interested in participating in international tenders and the majority of local production facilities in developing countries do not manufacture EPI vaccines, or cannot cover even current domestic demands. Measles and poliomyelitis bulk vaccines are not produced in developing countries, at all. In light of the expected increase in demand for EPI vaccines, the supply situation might become critical in the near future. Another result could be reduced price competition.

One possible way to prevent the occurence of such an event is the establishment and/or expansion of local production of vaccines in developing countries. This alternative is the preferred choice in all cases, where the starting material is the blood plasma from adult human donors. Another argument favouring local production is that vaccines with maximum expiration date can be supplied.

In the wider context of industrialization of developing countries, local production is obviously good to be pursued, particularly within a strategy based on more reliance on domestic resources. Within the pharmaceutical area, the production of immunizing agents has been identified as one of the most promising paths for increasing independence of developing countries.

10. GENERAL REQUIREMENTS AND ANALYSIS OF CENTRAL TECHNICAL ASPECTS OF THE PRODUCTION OF IMMUNIZING AGENTS IN DEVELOPING COUNTRIES

10.1 General Requirements of Production

It must be stressed at this stage that the principles of good manufacturing practice are summarized in a WHO document "General Requirements for Manufacturing Establishments and Control Laboratories" (Requirements for Biological Substances No.1 Revised 1965.)[29/] and should apply to all new or expanded production facilities.

Particular attention should be given to the recommendations contained in Part A, Section 1, regarding the training and experience of the persons in charge of production and testing as well as to the registration of such personnel with the national control authority.

The quality of immunizing agents should comply with the WHO requirements.

There are also national regulations which must be observed, for example, generally a special licence is required for the production of immunizing agents on a case-by-case basis.

10.2 Classification of Immunizing Agents in the WHO Revised Model List of Essential Drugs 1983

In order to analyse the technical aspects of the manufacturing processes involved in the production, biologicals for active immunization may be conveniently classified as follows:

(a) Bacterial vaccines, killed
    - Pertussis
    - Typhoid

(b) Bacterial vaccines, live, attenuated
    - BCG

29/ WHO Technical Report Series No. 323, p.11-22, 1966.

(c) Bacterial toxoids
- Diphtheria
- Tetanus

(d) Bacterial antigens
- Meningococcal vaccine

(e) Viral vaccines, inactivated
- Influenza
- Measles
- Poliomyelitis
- Rabies

(f) Viral vaccines, live
- Measles
- Poliomyelitis
- Yellow fever

10.3 Methodology of the Technical Analysis

Each of the above groups have peculiar technological aspects and should be manufactured in separate production facilities.

The general problems that have to be faced in the industrial production of toxoids and killed bacterial vaccines will be examined in some detail through the techno-economic analysis of some aspects of the manufacture of DPT vaccine.

The general aspects of the production of attenuated bacterial vaccines will be illustrated through the brief description of the manufacturing method of BCG vaccine.

The general aspects of the production of viral vaccines will be illustrated through the brief description of the manufacturing methods of Measles, Polimyelitis and Hepatitis B vaccines.

Biological products for passive immunization and diagnostic preparations will be discussed only by appreciation of some basic difficulties related to the establishment of such production.

10.4 Techno-economic Analysis of DPT Vaccine Production

The technical data of bulk DPT vaccine production in fermenters and in shaken or static cultures are given in Annex 5.

The general analysis of the data reveals that there is no conversion factor between the national and international units of potency, although the two corresponding values, e.g. $15x10^9$ bacilli (killed) and 4IU, are supposed to be expressions of the same basic quality requirement, the potency of the pertussis vaccine component of DPT.

It should also be mentioned that only the number of bacilli/ml can be measured during cultivation and the IU/ml results are confirmed after only 28 days. It has occured in practice that the same strain has produced $6x10^9$ and $5.5x10^9$ bacilli/ml in two subsequent cultivations and the corresponding IU values were 8.0 and 22.1, respectively.30/

It follows from these facts that the yields are not predictable, as far as IU values are concerned.

This example serves also to illustrate that national standards might differ from international specifications and a batch approved for the domestic market does not necessarily meet the WHO requirement, or vice versa.

10.4.1 Brief description of the production process

Diphtheria toxoid component

A suitable culture medium --Linggood or Mueller and Miller-- is prepared and a highly toxigenic, such as "Park-Williams 8" strain of Corynebacterium diphtheria is cultivated either in (i) Roux bottles, or (ii) fermenters. The culture filtrate is isolated and the diphtheria toxin is detoxified with formaldehyde. The toxoid is concentrated, e.g., by a molecular filtration device, and is subsequently purified by fractional precipitation with ammonium

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30/ Data received from a European manufacturer.

sulphate or trichloroacetic acid. A preservative, usually thiomersal, and an adjuvant such as aluminium phosphate are added. The production process is described in details in a WHO document.[31/]

Tetanus toxoid component

Tetanus toxoid must be produced in completely isolated premises and with separate staff and equipment. A suitable culture medium, such as improved Mueller amd Miller's medium is prepared and a highly toxigenic "Harvard" strain of Clostridium tetani is cultivated in either (i) 15-l bottles, or (ii) fermenters. Tetanus toxin in the isolated culture filtrate is detoxified with formaldehyde. After concentration by ultrafiltration, the toxoid is purified by fractional precipitation with ammonium sulphate. A preservative and an adjuvant are added. The process is described in details in a WHO document.[32/]

Pertussis vaccine component

A suitable culture medium, e.g., Cohen and Wheeler's medium, is prepared and Bordetella pertussis strains of the main serotypes should be cultivated either in (i) 1-l flasks, or (ii) fermenters. The 1-l flasks must be shaken during cultivation. The harvested bacterium mass is separated by centrifugation and resuspended in a buffered physiological sodium chloride solution. This bulk suspension is inactivated by keeping it at a temperature of 56°C for 30 minutes under constant stirring. Subsequently, a preservative and an adjuvant are added. The process is described in details in a WHO document.[33/]

31/ WHO Manual for the Production and Control of Vaccines. Diphtheria Toxoid: BLG/UNDP/77.1 Rev.1.

32/ WHO Manual for the Production and Control of Vaccines. Tetanus Toxoid: BLG/UNDP/77.2 Rev.1.

33/ WHO Manual for the Production and Control of Vaccines. Pertussis Vaccine: BLG/UNDP/77.3. Rev.1

DPT final bulk vaccine

The obtained bulk materials can be used for the preparation of DPT and DT combined vaccines by blending the finished final bulks of the single components.

The process for preparing DPT final bulk vaccine in fermenters is schematically illustrated on page 35, which shows also that quality control is integral part of vaccine production.

10.4.2 Effect of different demands on the utilization of Bulk DPT production capacity

The technological time requirements were calculated by using the technical parameters of the two cultivation processes described before and assuming the following data and conditions:

Population size	1,10 and 20 million
Birth rate	40/1000
DPT vaccination schedule	4x0.5 ml
Required excess production to compensate for production, distribution and administration wastage	47%
Continuous operation of production facilities in	3 shifts

The results are summarized in Tables XII and XIII. Table XII shows that the fermenter capacity utilization is satisfactory when the target population is 800,000. Table XIII shows that the cultivation process in static or shaken bottles, as described, cannot be used for a target population higher than approximately 550,000.

The general technical analysis of the two alternatives, cultivation in fermenters or bottles, leads to the following statements:

(a) Yields and quality of the final bulk toxoids and vaccine are better and more predictable if produced in fermenters.

Schematic illustration of a process alternative for preparing bulk DPT vaccine in fermenters

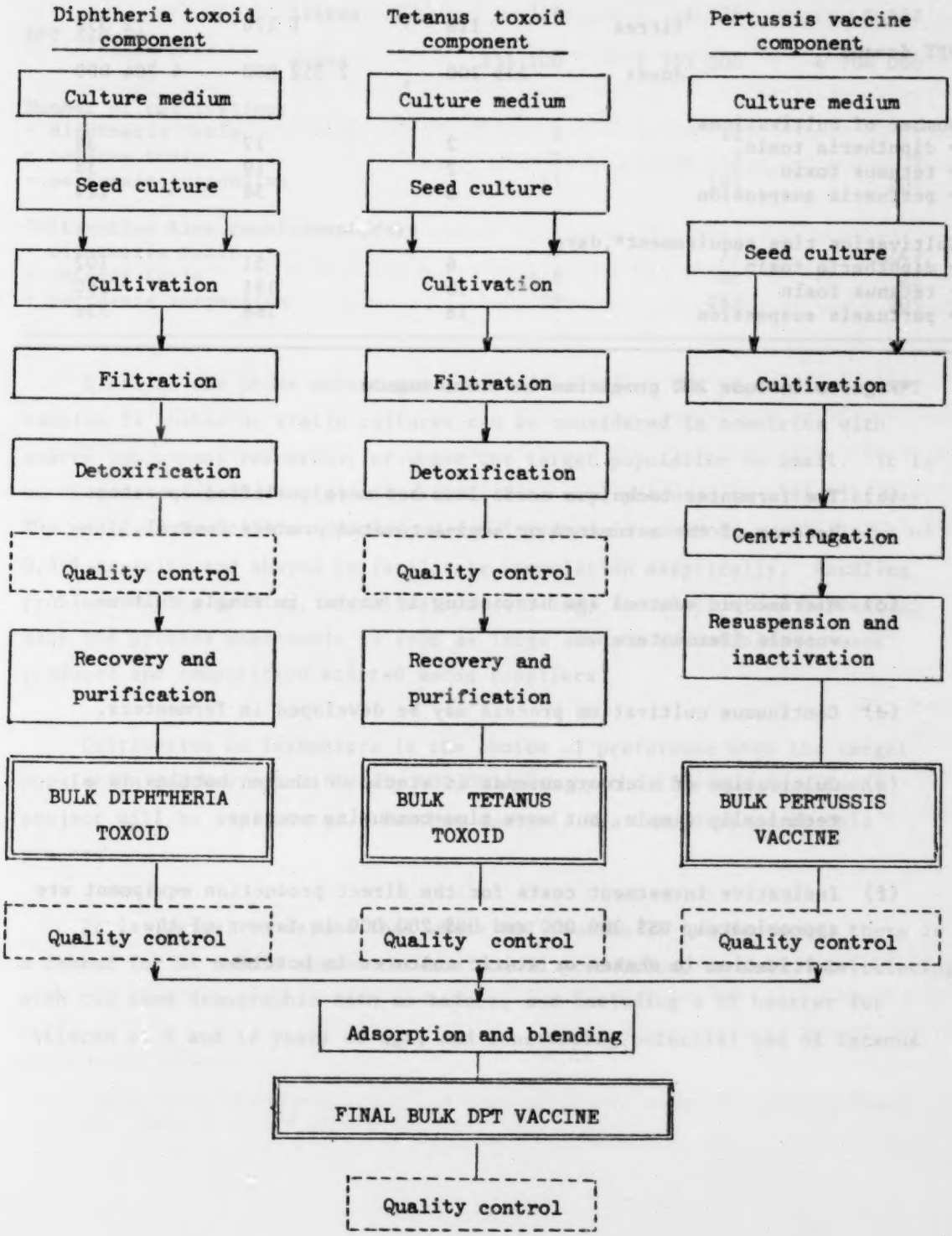

Table XII: Annual DPT Fermenter Capacity Planning for Different Target Population Sizes

Production variable		40 000	400 000	800 000
DPT demand	litres	118	1 176	2 352
	doses	235 200	2 352 000	4 704 000
Number of cultivations				
- diphtheria toxin		2	17	34
- tetanus toxin		2	19	38
- pertussis suspension		6	56	112
Cultivation time requirement*, days				
- diphtheria toxin		6	51	102
- tetanus toxin		18	181	360
- pertussis suspension		18	168	336

*Figures include 20% provision for maintenance

(b) The fermenter technique needs less but more qualified operators because of the automated or semi-automated process control.

(c) Microscopic control and harvesting is easier in single culture vessels (fermenters).

(d) Continuous cultivation process may be developed in fermenters.

(e) Cultivation of microorganismus in static or shaken bottles is a technically simple, but more time-consuming process.

(f) Indicative investment costs for the direct production equipment are approximately US$ 300,000 and US$ 200,000 in favour of the cultivation in shaken or static cultures in bottles.

Table XIII: Estimated Annual DPT Cultivation Times in Static or Shaken Bottles for Different Target Population Sizes

Production variable		40 000	400 000	800 000
DPT demand	litres	118	1 176	2 352
	doses	235 200	2 352 000	4 704 000
Number of cultivations				
- diphtheria toxin		1	11	21
- tetanus toxin		1	5	9
- pertussis suspension		11	101	202
Cultivation time requirement, days				
- diphtheria toxin		7	77	147
- tetanus toxin		8	40	72
- pertussis suspension		28	253	505

Based on the above advantages and disadvantages, the production of DPT vaccine in shaken or static cultures can be considered in countries with scarce investment resources, or where the target population is small. It is worth mentioning that originally antibiotics were produced in a similar way. The mould, a Penicillium species, was cultivated in numerous small flasks of 0.5-1 capacity and shaped to facilitate inoculation aseptically. Handling problems during washing, sterilization, filling, inoculation and harvesting made the process uneconomic as soon as large amounts of antibiotics were produced and competition started among suppliers.

Cultivation in fermenters is the choice of preference when the target population reaches approximately 400,000/year by the time the investment project will be implemented. Further analysis has been focused on this process.

It is logical to assume that where DPT vaccine is manufactured, there is a demand for DT toxoid and/or tetanus toxoid production, as well. Calculating with the same demographic data as before, and including a DT booster for children of 6 and 12 years of age, and considering potential use of tetanus

toxoid for special target populations such as pregnant women, injured persons and the army, an additional amount of 500,000 doses of diphtheria toxoid (4 cultivations, 12 days) and 1,400,000 doses of tetanus toxoid (12 cultivations, 102 days) would be required for a population of 10 million. Taking these figures into account, the cultivation time requirement is 63 days for diphtheria toxin and 283 days for tetanus toxin. Diphtheria toxin and pertussis suspension can be produced in the same fermenter; hence, their combined cultivation time requirement, 231 days, would result in a good capacity utilization, if a 5 work-day week is taken into account. In case of diphtheria toxin and pertussis suspension production this is possible, because the cultivation cycle is 2 days in both cases.

In case of tetanus, the capacity is not convertible, because both the equipment and the staff can exclusively be used for tetanus toxin production. The 77.5 per cent capacity utilization is acceptable anyway.

If DT toxoid and tetanus toxoid production is necessary also in case of the 20 million population, the additional cultivation time requirement is 22 days for diphtheria toxin and 196 days for tetanus toxin. The combined requirement for diphtheria toxin and pertussis suspension production is 482 days. Hence the capacity of two 50-litre fermenters could be exploited in a 5-day/week working schedule.

The 556 days of tetanus toxin production needs either consideration of larger fermenter sizes, or technical development of the process (higher operating volume, improvement of cultivation yields and/or recovery efficiency). At the investment stage, only the fermenter size can be changed. In the above example, a 100-l fermenter would solve the capacity problem.

10.4.3 Availability of materials for production

Fourty-nine analytical grade fine and specialty chemicals are used for the cultivation. All of them are available and none of them plays a key role in the direct material costs.

Good quality peptones should be used for the preparation of culture

media. Their share in the direct material costs might reach 30 to 40 per cent depending on the local availability of raw materials (casein, meat, and soya peptons).

10.4.4 Illustrative cost structure of the studied process

In the absence of specific figures, production costs could not be analyzed. All the same, the following cost structure permits structural analysis.[34/]

Cost element	Percentage in TPC	
Direct material costs		
fermentation	16	
recovery and purification	5	21
Conversion costs		
direct labour	15	
energy	7	
spare parts	9	
depreciation	5	36
Overheads		43
Total Production costs (TPC):		100

The direct material costs and import content are relatively small, hence the added value is high. On the other hand, this means that there is not much reserve for improvement of the direct material costs through better cultivation yields and/or recovery efficiency. The given elements of the conversion costs are also relatively stable, because of the 3-shift operation and continuous energy demand (machinery, equipment, cold rooms, etc.). The high overheads include costs of quality control with a share of approximately 20 per cent in the TPC. This dominant element of the TPC cannot be reduced, because the special breed test animals are expensive and the time demand of quality control is higher than that of the production itself. The profitability of production cannot be estimated from the above cost structure.

34/ Data received from a European manufacturer.

10.4.5 Other relevant information

For the protection of the environment, the production equipment (fermenters, glass vessels, devices, etc.) and the unused part of culture fluids must be sterilized. Only sterile effluents should be discharged into the public sewage system.

Animal housing must be built separated from the production premises.

Both equipment and staff involved in the production of tetanus toxin can be used exclusively for that purpose, hence this component of the investment should be very carefully planned to guarantee the most efficient capacity utilization.

Quality control plays a dominant role both in technical and economic aspects of DPT vaccine production. Another critical factor is the unpredictable occurence of production problems due to minor changes in the composition of the culture medium and/or process parameters (pH, temperature, aeration-agitation, etc.), or due to the reduced toxigenicity of the strains. Hence, the heads of the production and quality control department play a key role in the continuity of production.

10.4.6 Preparation of DPT vaccine starting from the final bulk

The preparation of DPT Vaccine (20 doses) in 10-ml vials, is similar to that of injections and includes the following operations: washing and sterilization of vials, rubber stoppers and aluminium caps, filling of the final bulk suspension into vials, sealing of the vials, visual inspection, printing and packing. Aseptic conditions should be guaranteed during the filling and sealing operations.

Taking a 250-l batch size and a labour-intensive, semi-automated technology into account the lead time of the production is approximately 70 days, of which quality control is 56 days. The 14 days production time can be reduced to 3 days, if modern injection making technique is used.

Before the product is released, government quality control approval might be required which also takes 56 days.

Hence the overall lead time of DPT vaccine production, including preparation of the final bulk, takes from 240 to 300 days, assuming that all quality control results are favourable and tests do not have to be repeated.

In the practice, delivery times are shorter than the overall lead time, because a final bulk can be kept under proper storage conditions for 2 to 3 years without affecting the quality and stability of the formulated vaccine.

Process economic calculations have not been performed because final bulk DPT price and the sales price of DPT vaccine for the same country were not available. Other elements of the packing - landed cost of packing materials, labor, depreciation, etc. - differ from country to country. All the same, it should be mentioned that quality control is indispensable also at this stage of backward integration and should be a dominant element of costing by analogy with the bulk vaccine production. On the other hand, existing injection making plants with free capacity for the preparation of multiple-dose vials improve the feasibility of local production starting from the bulk vaccine.

10.5 Brief Description of the Production Technique of Selected Vaccines

BCG vaccine (dried)

BCG vaccine is a dried, living culture of the bacillus Calmette-Guérin strain of Mycobacterium bovis.

Production of BCG vaccine, all operations up to and including sealing of the vaccine in ampoules, shall take place in completely self-contained premises with a separate staff to prevent contamination with virulent human tubercle bacilli.

The methods used for preparing killed and living bacterial vaccines are essentially the same.

Only the freeze-dried form possesses satisfactory stability, the expiration date being still not later than 1 year after the date of issue if stored at a temperature below 5°.

Control tests take minimum 6 weeks to complete.

Poliomyelitis vaccine

There are three distinct antigenic types of poliomyelitis virus, types 1, 2 and 3. The three types of virus are grown separately in monkey-kidney or in human diploid-cell cultures. Only Macaca or Cercopithecus monkeys may be used.

The production shall be conducted by a separate staff immune against polio virus.

The live, attenuated oral vaccine is produced by attenuated Sabin strains in a fermenter combined with a microcarrier culture system. The virus suspension is harvested, the remnants of tissue cells are removed by filtration. The univalent vaccines are blended to give the trivalent product. Very large samples are tested for safety.

The inactivated, parenteral vaccine is manufactured in essentially the same way except that the harvested and filtered viral suspension is inactivated before blending the univalent vaccines.

The expiration date for frozen live, attenuated oral vaccine is not later than 1 year after date of issue from manufacturer's cold storage. The expiration date for liquid vaccine is not later than 30 days after the issue from manufacturers cold storage.

The expiration date of inactivated vaccine is not later than 1 year after date of issue from manufacturer's cold storage, if kept at a temperature of $5^{\circ}C$.

Measles vaccine

Measles vaccine is a sterile preparation of the attenuated measles virus grown in various types of primary, such as chick-embryo, dog-kidney or monkey-kidney tissue cultures.

The method of preparation is similar to that used for the live, attenuated poliomyelitis vaccine.

The minimum expiration date is not later than 1 year after the date of manufacture, if kept at a temperature of -20°C.

Hepatitis B vaccine

The starting material for the purified hepatitis B virus or Dane particle (HBV) of the manufacturing process is a fluid containing a surface antigen, HB_sAg. The fluid may be any human biological fluid containing HB_sAg, such as plasma, saliva, fecal extracts, nasal pharyngeal secretions, bile, spinal fluid, sweat, urine, semen, vaginal secretions or menstrual blood. The plasma is obtained in conventional manner, e.g., by plasmaphoresis.35/

A complex series of inactivation and purification is required to produce the vaccine. It takes 65 weeks to manufacture and test each lot.

National Institutes of Health scientists in Maryland, U.S.A., have successfully tested a novel hepatitis B vaccine in rabbits. The vaccine is produced by grafting the hepatitis virus surface antigen onto vaccinia virus using the techniques of genetic engineering.36/

Several patents have been published which describe processes relating to hepatitis A and hepatitis B antigens and to methods for their preparation and for the preparation of hepatitis vaccines.37/

10.6 Other Relevant Information on Vaccine Production Techniques

All the six EPI vaccines can be produced in the same type of fermenters and essentially with the same technique. Operational parameters, such as stirring speed might be different for each product, of course.

35/ U.S. Patent 4,129,646; December 12, 1978.

36/ SCRIP No. 791, May 4th 1983, p.17

37/ J.I. Duffy: Vaccine Preparation Techniques, Noges Data Corporation, Park Ridge, New Jersey, U.S.A. (1980).

The size of the fermenters ranges from 7.5 to 350 litres. The small fermenters are generally made of glass and can be assembled locally.

The fermenter size primarily depends on the production capacity of the strain and the cultivation cycle. However, other factors such as costs of quality control and risk of contamination should also be taken into account.

Cholera, meningococcal, staphylococcal and typhoid cultures can be produced by the same technique. The purification of meningococcal polysaccharide vaccine needs additional equipment, of course.

On the other hand, fermenter capacities are mostly not convertible and some equipment can exclusively be used for the manufacture of a single product.

The production processes require control of the entire environment so that cultivation proceeds efficiently and, more importantly, so that it can be repeated exactly to result in the same quality and quantity of product.

The above statements serve to illustrate that the technical parameters and their reproducibility play an essential role in the process economics and should be taken into account when comparing alternative offers for transfer of technology or preparing feasibility studies for investment projects. They also indicate that there is an economic reserve in the production techniques that can be exploited by applied research and development. Technical research is justified also for ad hoc production problem analysis and it is a pre-requisite for the introduction and integration of process improvements and new products into the manufacturing programme.

10.7 Sera and Immunoglobulins

The products for passive immunization are either whole serum or concentrated immune globulins of human or animal origin. They are used in the immediate prophylaxis, treatment or modification of specific disease states. Human normal immunoglobulin is the only non-specific product in this category.

Antitoxins are sterile solutions of antibodies obtained from the serum of animals, usually horses, that have been hyperimmunized against a specific

toxin. Diphtheria antitoxin and Tetanus antitoxin pertain to this group of immunizing agents.

Antivenins may be included among the antitoxins. They are obtained from the serum of healthy horses hyperimmunized against venoms of poisonous reptiles or spiders.

Artirabies hyperimmune serum is produced essentially in the same way.

Human immune blood derivatives are exemplified by Anti-D Immunoglobulin and Normal Immunoglobulin in the WHO Revised Model List of Essential Drugs 1983.

The major technical constraint in the manufacture of products for passive immunization is that immune globulines are produced in animals or humans and only the purification and concentration are performed by industrial methods. Human immune globulines are preferred to equine products, but the collection of blood from specifically immunized adults requires high-degree organization and is very expensive.

10.8 Diagnostic Antigens

Diagnostic antigens are used (a) to test the susceptibility or immunity of a target population to a particular infection, (b) to determine the antibody titer of immunized individuals, and (c) to detect the presence of a disease at a very early stage when clinical symptoms have not manifested themselves.

Tuberculin purified protein derivative (PPD), a representative of this group, is included in the WHO Revised Model List of Essential Drugs 1983. It is used to identify target population for BCG vaccination or to measure the success of immunization.

The manufacturing process includes the following steps: growing Mycobacterium tuberculosis in a synthetic medium, removal of the bacteria by filtration, removal of components of the culture medium by ultra-filtration, precipitation and purification of the protein, and preparation of a (a) concentrated PPD with 50% aqueous glycerin solution, or (b) diluted PPD, which can also be freeze-dried.

Expiration date varies between 1 year at 5° (diluted PPD) and 2 years at 5° (concentrated PPD) and at 30° (freeze-dried PPD).

10.9 Conclusion of the Techno-economic Analysis of the Manufacturing Processes

The production of conventional vaccines in fermenters is technically feasible in developing countries. Source materials and technology for manufacture are available. The added value of domestic production is higher than 50 per cent.

Principal factors that affect economic feasibility of production include costs of present vaccine supplies, size of the domestic target population and costs of quality control. Special attention should be paid to planning production capacities which are not convertible due to regulatory requirements.

Expertise in production management is a critical element of the continuous operation of the manufacturing plant.

11. AVAILABILITY AND TRANSFER OF TECHNOLOGY

11.1 Availability of Technology

In an attempt to assess the availability of technology for vaccine production, enquiries were sent to 104 addresses[38/] in the course of this study with the request of declaring willingness of transfer of technology under mutually acceptable conditions. 32 replies have been received by the time of writing the study, 23 from industrialized and 9 from developing countries.

The 20 positive replies for transfer of technology for immunizing agents included in the WHO Revised Model List of Essential Drugs 1983 are summarized in Tables XIV, XV, and XVI.

38/ International List of Availability of Vaccines, WHO-BLG-80.1.

Table XIV: Availability of Technology for the Production of Vaccines for Universal Immunization

Supplier's number in Annex 6	BCG	DPT	DT	Measles	Polio	Tetanus
1.	+	-	-	-	-	-
2.	-	+	+	-	+	+
3.	+	+	-	-	-	+
4.	+	+	+	-	-	+
5.	+	+	+	+	+	+
6.	-	+	+	-	-	+
7a.	+	+	+	+	-	+
7b.	-	+	+	-	-	+
8.	-	+	+	-	-	+
9.	+	+	+	-	+	+
10.	-	+	+	+	+	+
12.	+	+	+	+	+	+
14.	+	-	-	-	-	-
15.	-	+	+	-	-	+
16.	-	+	+	-	-	+
17.	+	+	+	-	-	+
18.	+	-	-	-	-	-
20.	+	-	-	-	-	-

Key: + = Technology available - = technology not available

Note: Various strengths and presentations of vaccines, e.g. adsorbed or non-adsorbed, for adults or for children, etc. have been disregarded in this table.

Table XV: Availability of Technology for the Production of Vaccines for Specific Groups of Individuals

Supplier's number in Annex 6	Influenza	Meningococcal	Rabies	Typhoid	Yellow fever
2.	+	-	-	+	-
3.	-	-	-	+	-
4.	+	-	-	+	+
5.	+	+	+		+
6.	-	-	+	-	-
7.(a)	+	-	-	-	-
8.	-	-	-	+	-
9.	+	-	-	-	-
10.	+	+	-	+	-
11.	-	-	+	+	-
12.	+	+	+	-	-
13.	-	-	+	-	-
16.	-	-	+	-	-
17.	+	-	+	-	-
18.	-	-	+	+	-
19.	-	-	+	-	-

Table XVI: Availability of Technology for the Production of Sera and Immunoglobulines

Supplier's number in Annex 6	Human anti-D IG	Anti-rabies serum	Antivenom sera	Diphtheria antitoxin	Human normal IG	Tetanus antitoxin
5.	-	-	-	+	-	-
8.	-	-	-	+	+	+
10.	+	-	+	+	+	+
11.	-	-	+	-	-	-
12.	-	-	-	-	+	+
13.	-	+	+	-	-	-
17.	-	+	+	+	+	+
18.	-	-	+	-	-	-
19.	-	+	-	-	-	-

Tables XIV, XV, and XVI should be used together with Annex 6, which is a directory of manufacturers that have confirmed willingness to transfer of technology.

Offers have been received also for immunizing agents and diagnostic antigens not listed in Tables XIV, XV and XVI. Specific enquiries should be sent to the address given in Annex 6.

The remaining balance of 12 replies can be classified as follows:

Positive, only diagnostics	2
Negative	2
Negative, but offers technical assistance in quality control problems	1
Discontinued production	1
Needs further action	6

Although the survey has not yet been completed, it already shows that technology is available for the production of essential vaccines and sera in developing countries.

11.2 Transfer of Technology

The commercial-scale transfer of technology for the production of immunizing agents has a few aspects which should be given special consideration in the contractual arrangements:

- long-term technology transfer commitment should be preferred to the execution of a single project and this could be expressed in a separate co-operation agreement;

- technology should be adapted to the use of local raw materials in the cultivation to the maximum possible extent;

- training of the persons in charge of production and of those assigned to various areas of responsibility in the manufacturing establishment should be ensured also in the recipients premises for a period not less than one year;

- supplier of technology should declare experience both in technology and in the design, construction and operation of commercial-scale production units.

Transfer of technology on the laboratory or pilot-plant scale level, or as a single transaction, should be considered only by such manufacturers that have minimum 10 years of industrial experience and a well equipped and staffed in-process control and development laboratory. These manufacturers have also the option of following published research and development activities of interest and applicability to their products, and elaborating the relevant technology without resorting to licencing. The patent implications of this alternative must be taken into account, of course.

Transfer of technology for products manufactured from human blood as a starting material should be facilitated by the fact that owners of the technology cannot meet always the demand of their domestic market and business interests are not at stake because export of such products is restricted on ethical grounds, as well.

12. RESEARCH AND DEVELOPMENT

Modern industry cannot exist without constantly developing new and improving existing technologies.

Technology development passes through three definite, distinct phases: research, development and commercialization. It should be recognized that the most important intangible capital of a manufacturer is what is referred to as "know how" and it comes from all phases of technology development.

It is also expedient to distinguish between pure, basic, or academic research, done without any concern of the use which might be made of the results, and applied or industrial research, done to produce more information for the continuation of a development programme.

Development, followed by the engineering design both of the product and its manufacturing system, brings improved or new goods to the market.

Industry should mainly be involved in applied research and technology development, always with a clear practical goal and objective in mind.[39/]

39/ Based on excerpts from UNIDO/IO.381/Rev.1, 10 Nov. 1981.

12.1 Basic Research

Biotechnological industries together with electronics industries will make the third major industrial revolution.

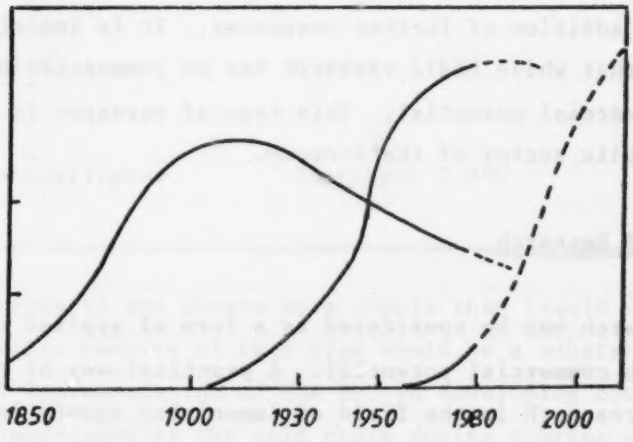

Figure 3: The three major industrial revolutions
(Coal industry and railroads, Chemical and oil industry,
Electronics and biotechnological industries)

The biotechnological industrial revolution is the result of scientific discoveries which have increased knowkedge in basic life processes at the molecular, cellular and genetic levels.

The pharmaceutical industry has been the first to recognize the potentials of genetic engineering which has opened up new approaches, among others, of vaccine development. Molecular cloning may produce technical solutions to the biosynthesis of specific antigens against malaria, schistosomiasis, filariasis, trypanosomiasis, leishmaniasis, leprosy, to mention only a few examples of diseases prevailing in developing countries.

Novel analytical techniques based on selective adsorption, electrophoresis, countercurrent distribution and isotope-dilution methods have contributed to the development of biochemistry to a great extent.

Computers have opened up new horizonts also in pharmaceutical applied research.

The product of basic research is knowledge, a public good, which can be utilized without the addition of further resources. It is important to emphasize, however, that while basic research has no commercial objectives, it may have clearly commercial potential. This type of research is usually undertaken by the public sector of the economy.

12.2 Industrial Research

Industrial research may be considered as a form of applied research which tackles problems with commercial potential. A practical way of reviewing some areas of industrial research in the field of immunizing agents is to divide products into "improved" and "new" categories.

Improved vaccines

Improved thermostability of immunizing agents plays an important role in the successful implementation of vaccination programmes. The following table summarizes the shelf-life data of selected vaccines as recommended by various producers:

Table XVII: Stability data of some vaccines at different storage temperatures (degrees Celsius)

Product	Temperature	
	recommended	other
BCG vaccine, dried	1 year, 4-8°C	4 weeks, 37°C
DT, absorbed	2-3 years, 4-10°C	6 months, 30°C 1 month, 37°C
DPT, adsorbed	18-30 months, 4-8°C	4 months, 24°C 1 month, 37°C
Polio, oral	3-6 months, 2-8°C	2 years, -20°C 7-14 days, + 20°C
Measles, dried	1 year, 2-4°C	2 years, -20°C 1-4 months 20°C 5-14 days, 37°C
Measles, reconstituted	24 hours, 2-8°C	7 hours, 37°C

Freeze dried products are always more stable than liquid vaccines, and a combined DPT-Polio vaccine of this type could be a substantial contribution to the successful implementation of the EPI in developing countries through reducing the importance of the cold chain during storage and distribution.

The composition of the conventional vaccines is not well defined and their quality is usually tested in comparison with standards and/or reference preparations. The main reason of this phenomenon is that basic parts of the current process of technology, such as cultivation and inactivation, were developed a long time ago using mostly potency and toxicity tests to define quality. Hence, these preparations sometimes contain many unidentified components in addition to the protective antigen(s). The impurities might be responsible for adverse reactions and they can be eliminated by controlling the cultivation and by applying modern techniques of purification in the recovery stage.

Patients generally prefer oral dosage forms to injections. The use of oral dosage forms might be justified also on medical grounds, for instance, an oral pertussis vaccine has been reported to be at least as effective as parenteral vaccination and no adverse reaction was observed in field trials with 15,000 newborns.

Packaging improvements such as disposable syringes reduce risk of contracting hepatitis, but this component itself might represent approx. 20 per cent of the total production costs of the dosage form manufacture.

The above examples illustrate that improved vaccines offer advantages mainly in reducing risks associated with the use of conventional vaccines. These advantages should be contrasted with increased costs of the vaccine component and the cost of changes in the implementation of the vaccination programme.

Novel purified vaccines based on chemically defined antigens have been introduced into the medical practice during the past decade. An example is Meningococcal polysaccharide vaccine.

Meningococcal polysaccharide vaccine

The presently available Group A vaccine is effective in all age groups, but Group C vaccine does not elicit sufficient antibody production in children below 2 years old, whereas morbidity and mortality are the highest in this age group. Epidemics produced by other serogroups (e.g. B, W135, etc.) also occur. Research is in an advanced stage to solve these problems and technology might include modification of the antigen.

New vaccines

For some widespread diseases, such as amoebic disentery, basic knowledge is not enough to elaborate a research programme. For others, preliminary experimental evidence suggests that a useful vaccine could be produced (Table XVIII) if technical solution is found to the production of the antigen making it available for clinical trials in sufficient quantities and at low costs.

Table XVIII: Major diseases for which vaccines could be developed

Parasitic diseases	Viruses	Bacteria
Filariasis	Hepatitis A, non-A:non-B	Gonococcal vaccine
Leishmaniasis	Herpes simplex	Leprosy
Malaria	Respiratory syncytial	
Schistosomiasis	Varicella-zoster	
Trypanosomiasis		

Vaccines prepared from purified human lung cancer antigens appear to prolong patient's survival.

Some research activities for new products can be illustrated through selected examples.

Antileprosy vaccine

A vaccine against leprosy is being developed at the Cancer Research Institute in India. A mycobacterium isolated from human leproma was found to have many antigens in common with mycobacterium leprae, including those involved in cell-mediated immunity. Lepromin conversion was observed in 50% of the lepromatous leprosy patients studied and in 80% of the borderline patients four months after vaccination. Multicentre field trials of the new vaccine are now planned, it is reported.40/

Malaria vaccine

Immunization attempts using a variety of plasmodial preparations have identified several developmental stages and vaccination procedures which can protect against malaria. Earlier approaches to malaria immunization were based primarily on the use of intact, attenuated parasites as immunogen.

40/ SCRIP, No. 701, 14 June 1982.

The emphasis of recent research is on the identification and characterization of antigens which induce a protective response in the immunized host.[41/]

Genetic engineering

Several UNIDO studies have been written on the implications of genetic engineering and biotechnology on industrialization in developing countries.

Two of them are dedicated to the application of genetic engineering for the development of vaccines against major human and animal diseases in the developing countries.[42/][43/] Both these documents and other sources of literature emphasize that the new technologies of genetic engineering could definitively open up large avenues for improving the living standards and the quality of life for the whole humanity, in particular the large masses in the developing countries.

Genetic engineering will have an impact on the improvement of the safety of existing products, but more importantly it offers the only technical solution to the wide-spread use of vaccines produced from raw materials of limited availability. In certain cases, genetic engineering is the only possibility to develop vaccines against diseases with high mortality.

It is not likely that commercial-scale production technologies of vaccines in developing countries are going to be affected by genetic engineering during the forthcoming decade. If such a technology is developed, however, it could probably be transferred easily because genetically

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41/ R.S. Nussenzweig: Vaccination against malaria: use of monoclonal antibodies for the characterization of the protective antigens, Pontificiae Academiae Scientiarum, Scripta Varia 47, pp.33-37, 1982.

42/ UNIDO/IS.273 of 30 December 1981: The Potential of Genetic Manipulation for the Improvement of Vaccines against Animal Diseases in Developing Countries.

43/ UNIDO/ID/WG.382/2/Add.4 of 20 September 1982: Application of Genetic Engineering and Biotechnology for the Production of Improved Human and Animal Vaccines with Particular Reference to Tropical Diseases.

manipulated microorganisms can be grown in the same fermenters and with approximately the same technical standard as described in Chapter 10. Hence, the establishment of a production plant for bacterial vaccines should also be seen as an investment for the transfer of new biotechnologies.

12.3 Financing of Research

Many of these diseases are particularly prevalent in the developing regions, but neither the financial resources nor the necessary expertise is available for a broad-scale research and development programme for new vaccines.

WHO's Special Programme for Research and Training in Tropical Diseases (TDR) was adopted in 1976 and had been funded to the value of over US$ 90 million until 1981 with a 1981-82 budget of US$ 26,579,000. Malaria and leprosy vaccine development are included among the many projects in the TDR. Both projects are in the preclinical phase, although uncontrolled positive clinical studies have also been conducted with antileprosy vaccine in small human populations.

A selected number of companies has spent over US$ 100 million in research into tropical diseases between 1977 and 1980.[44/]

Whereas these activities are regarded as very valuable contribution to the treatment of tropical diseases, it should be mentioned that resources are concentrated on the development of new chemotherapeutic agents rather than vaccines.

It is also worth mentioning that the development of one new drug in industrialized countries might cost as much as US$ 100 million.

Hence, the current financial resources allocated to R&D activities on vaccines against tropical diseases are not in proportion with the potential

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44/ Pharmaceuticals in Developing Countries, Papers presented at the 11th IFPMA Assembly, 7/8 June 1982, p.41.

social benefits of the projects. In other words, the clinical need is large enough to justify investment which does not seem to be attractive from the viewpoint of returns.

One possible solution to this problem could be the involvement of public sector organizations in industrial research and development for new pharmaceuticals and/or offering tax incentives for the industry involved in such projects.

The inclusion of selected projects in the research programme of the International Centre for Genetic Engineering and Biotechnology[45/] would offer an alternative for government involvement in funding R & D activities in such a way as to share both the risks and benefits on an international scale.

If a new vaccine would become available for the treatment of diseases in TDR, the social, economic and political impacts of a decrease in mortality and morbidity would be significant and the effects would be felt on the global level.

13. SUMMARY OF THE MAJOR FINDINGS

Social cost-benefit and cost-effectiveness studies conclude that immunization against infectious diseases can be among the most beneficial investments in developing countries.

Developing countries as a group constitute large markets for immunizing agents, in particular for EPI vaccines.

Every 1990 and 2000 scenario indicates that all the potential increase in EPI vaccine demand is expected in the developing regions.

A significant number of manufacturers in industrialized countries has withdrawn completely or partially from the conventional vaccine field.

45/ UNIDO/IS.254 of 9 November 1981: The Establishment of an International Centre for Genetic Engineering and Biotechnology.

The increasing demand and the reducing number of suppliers causes concern that availability of EPI vaccines in developing countries might become critical during the forthcoming years.

One possibility to prevent such an occurence is the establishment and/or expansion of local production for immunizing agents in developing countries. There are also strong arguments for domestic production from the points of view of industrialization and greater self-reliance.

Analysis of the production techniques of selected bulk toxoids and vaccines has revealed that local production of EPI vaccines in fermenters is technically feasible and materials for production are available from multiple sources.

Quality control is a dominant element of the total production costs. Direct material costs and hard-currency content of other fixed and variable costs are relatively low, approximately 30 to 40%, hence added value is higher than usual.

Expertise in production management and quality control are critical elements of both project implementation and continuous operation of the production plant.

Sterilized effluents do not create environment pollution problems.

The techniques used in filling and sealing of the bulk toxoids and vaccines into ampoules or vials as well as freeze drying are similar to those applied in injection making.

Economic barriers to entry into the EPI vaccine production in developing countries are the size of the domestic target population, low profit margin and capacity utilization limited by regulatory requirements.

Barriers to entry into vaccine production for special target populations include availability of source materials (strains, cell lines for culture

broths, and human plasma for antigens and immune globulins), high-level technology and patents.

Applied research for process development is a prerequisite of technical self-sufficiency and future availability of high technology vaccines.

Research for new vaccines for the treatment of diseases prevailing in developing countries requires involvement of the public sector in industrial research and creation of incentives for current manufacturers to justify investment in the development of new products for which the health demand is large.

Genetic technologies offer new approaches for vaccine development. They will compete with current vaccine manufacturing techniques and, for certain vaccines, genetic engineering is the only possibility to ensure unlimited supply.

14. CONCLUSIONS AND RECOMMENDATIONS

Some aspects of the global problems related to the use of immunizing agents in the prevention of diseases, have been reviewed to assist developing countries in the establishment and expansion of local production facilities for biologicals.

The study has been focused on the assessment of the demand for conventional vaccines as well as for the identification of barriers to entry of their production in developing countries. Some important factors affecting the subject such as Good Manufacturing Practice, regulatory issues, health infrastructure for distribution, etc. have been tackled only tangentially because these issues have regularly been discussed at different forums related to the EPI.

The following conclusions have been drawn from the major findings of the study:

(a) The importance of biological production is likely to be underestimated by the developing countries. The advantages should be weighed against the disadvantages on a country by country basis and technical factors should be taken into account when preparing economic feasibility studies.

(b) Other factors, such as self-sufficiency in this important field of public health as well as availability of high-technology vaccines should also be considered in the decision-making process, otherwise the gap in the quality of health services between industrialized and developing countries will widen and developing countries will not be able to profit from scientific developments in this important field of medicine.

(c) Industrialized countries would also profit from the eradication of an infectious disease and this aspect should make international co-operation easy.

(d) Transfer of science should go along with transfer of technology. Improved or new vaccines can be developed mainly through international co-operation, since the clinical investigations should be carried out in the developing countries where the disease is prevalent, whereas chemical, bio-technological and preclinical expertise is available mainly in industrialized countries where the occurence of the disease is very low or nil. Hence, transfer of science and technology is not only a moral issue, but a mutual interest of both parties.

The alternative strategies for countries to develop a local production can practically be limited to investment, licensing and various forms of joint ventures.

The investment strategy may be the preferred choice for countries that have or can build up pharmaceutical industrial companies with experience in biotechnology and parenteral dosage-form manufacture that have diversification plans into the vaccine field. Such manufacturers could establish the complete vertical integration starting from the production of bulk toxoids and vaccines, and would also have the necessary industrial infrastructure required for smooth operation. These manufacturers have also the option of using published information to elaborate their own technology without resorting to licensing.

The licensing strategy for the production of conventional vaccines might apply to countries having companies without biotechnological history and experience but with existing production facilities for injection making. The pre-requisite for this option is a long-term technical co-operation agreement that provides assistance for the elaboration of the optimum process parameters and training of managers in the licensee's premises during the first year of operation and in the licensor's premises for 2-4 weeks in each subsequent year for a period of not less than 5 years.

Production of vaccines can be started with the preparation of the vaccine from the final bulk and extending vertical integration to cultivation in fermenters when management is convinced of the feasibility of the new line. An advantage of this option is that additional investment can be kept to a minimum to establish the quality control facilities. The pre-requisite for this option is a long-term supply agreement with provision for conditions of future vertical integration and right of first refusal for product-related innovations.

Joint venture is the alternative which could be considered primarily when companies have no experience either in biotechnology or injection manufacture.

Whatever strategy is selected, it is important to appreciate that vaccines are urgently needed to save millions of lives each year.

Annex 1

Biological products in the WHO revised model list of essential drugs[a/]

1. Sera and immunoglobulins
   - 1.1 Anti-D immunoglobulin (human)
   - 1.2 Antirabies hyperimmune serum
   - 1.3 Antivenom sera
   - 1.4 Diphtheria antitoxin
   - 1.5 Immunoglobulin, human normal
   - 1.6 Tetanus antitoxin

2. Vaccines for universal immunization
   - 2.1 BCG vaccine (dried)
   - 2.2 Diphtheria-pertussis-tetanus vaccine
   - 2.3 Diphtheria-tetanus vaccine
   - 2.4 Measles vaccine
   - 2.5 Poliomyelitis vaccine (live attentuated)
   - 2.6 Tetanus vaccine

3. Vaccines for specific groups of individuals
   - 3.1 Influenza vaccine
   - 3.2 Meningococcal vaccine
   - 3.3 Rabies vaccine
   - 3.4 Typhoid vaccine
   - 3.5 Yellow fever vaccine

4. Diagnostic agents
   - 4.1 Tuberculin, purified protein derivative (PPD)

5. Plasma fractions for specific uses
   - 5.1 Albumin, human normal
   - 5.2 Antihemophilic fraction (dried)
   - 5.3 Factor IX complex (dried)

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a/ The use of essential drugs (WHO Technical Report Series, No. 685, 1983)

Annex 2

Brief Description of the Model Used to Estimate Vaccine Demand

Denote

P_t... total population in

t..... year;

P_v... part of the population that does not require vaccination (e.g., target population is a special group of the society and other members of the population are not vaccinated);

P_T... target population, equal to $(P_t - P_v)$;

B_t... number of additions to be target population (i.e., the number of newly born surviving to vaccination age);

n_t... $= n_{St} + n_{Bt}$ = number of starting doses plus number of boosters;

C_{St}.. proportion of target population to be vaccinated for the first time in year t;

C_{Bt}.. proportion of target population requiring booster;

W..... number of wasted doses;

w..... fraction of wasted doses, $\frac{W}{n_t}$ during administration of the vaccines from multiple-dose containers;

D..... total demand for a selected vaccine.

c..... coverage of the target populations

The total number of doses required in year t is:

$$n_t + W = n_t + n_t.w = n_t\ (1 + w)$$

Assuming that all additions to the target population are to be vaccinated:

$$n_{St} = C_{St} \cdot P_T + B_t,$$

and

$$n_{Bt} = C_{Bt} P_T,$$

hence

$$n_t = P_T\ (C_{St} + C_{Bt}) + B_t$$

and accounting for the wastage, the total demand, D, is:

$$D = c\left\{P_T\left[(C_{St} + C_{Bt}) + B_t\ (1 + w)\right]\right\}$$

Annex 3

Annual mid-year population, medium variant 1980, 1990 and 2000[a/] by UNITAD regions

Region	Population in thousands 1980	1990	2000
1. NORTH AMERICA	247 717	273 650	295 328
Canada	24 484	28 178	31 499
United States of America	223 233	245 472	263 829
2. WESTERN EUROPE	420 384	442 024	462 629
Austria	7 481	7 441	7 425
Belgium	9 833	9 905	9 964
Cyprus	620	654	682
Denmark	5 122	5 195	5 249
Finland	4 863	5 020	5 058
France	53 508	54 970	56 252
Germany, Fed. Rep. of	60 931	59 622	58 822
Greece	9 329	9 886	10 395
Iceland	231	254	274
Ireland	3 308	3 694	4 118
Israel	3 937	4 828	5 619
Italy	56 940	58 427	59 108
Luxemburg	358	355	349
Malta	343	370	390
Netherlands	14 079	14 682	15 180
Norway	4 079	4 203	4 312
Portugal	9 836	10 531	11 154
Spain	37 378	40 541	43 362
Sweden	8 274	8 199	8 088
Switzerland	6 466	6 493	6 461
Turkey	45 254	57 336	69 991
United Kingdom	55 886	55 479	55 208
Yugoslavia	22 328	23 939	25 168
3. CPE EUROPE	378 249	409 782	435 482
Albania	2 732	3 350	3 885
Bulgaria	9 007	9 413	9 698
Czechoslovakia	15 336	16 078	16 839
German Democratic Rep.	16 854	16 913	16 915
Hungary	10 754	10 912	10 964
Poland	35 805	38 967	41 217
Romania	22 268	23 994	25 728
USSR	265 493	290 155	310 236
4. JAPAN	116 551	123 185	129 282

(continued)

a/ Demographic Indicators of Countries: Estimates and projections as assessed in 1980, United Nations ST/ESA/SER.A/82, New York, 1982

Annual mid-year population, medium variant 1980, 1990 and 2000[a] by UNITAD regions (continued 1)

Region	Population in thousands 1980	1990	2000
5. OTHER DEVELOPED	47 041	58 838	73 139
South Africa	29 285	39 018	51 320
Australia	14 488	16 170	17 795
New Zealand	3 268	3 650	4 024
6. LATIN AMERICA	358 229	452 449	558 050
Argentina	27 036	30 277	33 222
Bahamas	n.a.	n.a.	n.a.
Barbados	263	292	320
Bolivia	5 570	7 314	9 724
Brazil	122 320	153 171	187 494
Chile	11 104	13 061	14 934
Colombia	25 794	31 820	37 999
Costa Rica	2 213	2 776	3 377
Cuba	9 732	10 540	11 718
Dominican Republic	5 947	7 534	9 329
Equador	8 021	10 949	14 596
El Salvador	4 797	6 484	8 708
Guatemala	7 262	9 676	12 739
Guyana	883	1 069	1 238
Haiti	5 809	7 509	9 860
Honduras	3 691	5 105	6 978
Jamaica	2 188	2 535	2 872
Martinique	325	337	362
Mexico	69 752	91 976	115 659
Nicaragua	2 733	3 778	5 154
Panama	1 896	2 346	2 823
Paraguay	3 168	4 231	5 405
Peru	17 625	23 355	30 703
Surinam	388	527	698
Trinidad and Tobago	1 168	1 337	1 483
Uruguay	2 924	3 166	3 448
Venezuela	15 620	21 284	27 207
7. AFRICA (South Sahara)	330 891	450 878	614 259
Angola	7 078	9 285	12 376
Benin	3 530	4 861	6 756
Botswana	807	1 123	1 597
Burundi	4 241	5 516	7 207
Central African Republic	2 294	2 965	3 914
Chad	4 455	5 558	7 063
Comoros	358	476	620
Congo	1 537	2 030	2 717
Ethiopia	31 468	41 259	54 666
Equatorial Guinea	363	468	613

(continued)

Annual mid-year population, medium variant 1980, 1990 and 2000[a] by UNITAD regions (continued 2)

Region	Population in thousands 1980	1990	2000
7. AFRICA (South Sahara)(continued)			
Gabon	548	640	754
Gambia	603	788	1 046
Ghana	11 679	16 214	22 348
Guinea	5 014	6 609	8 823
Guinea Bissau	573	693	859
Ivory Coast	8 034	10 964	14 775
Kenya	16 466	24 831	37 138
Lesotho	1 341	1 726	2 222
Liberia	1 967	2 821	4 002
Madagascar	8 742	11 545	15 208
Malawi	6 162	8 634	12 014
Mali	6 940	9 290	12 620
Mauritania	1 634	2 207	3 022
Mauritius	959	1 117	1 248
Mozambique	10 473	13 895	18 701
Namibia	1 009	1 360	1 822
Niger	5 318	7 278	10 045
Nigeria	77 082	107 954	149 965
Reunion	525	604	685
Rwanda	4 797	6 660	9 333
Senegal	5 661	7 430	9 747
Sierra Leone	3 474	4 606	6 090
Somalia	4 637	5 938	7 156
Swaziland	557	754	1 020
Togo	2 625	3 577	4 844
Uganda	13 201	18 262	25 396
United Rep. of Cameroon	8 444	10 838	13 937
United Rep. of Tanzania	17 934	24 774	34 031
Upper Volta	6 908	9 067	11 895
Zambia	5 766	8 079	11 276
Zaire	28 291	37 693	49 982
Zimbabwe	7 396	10 489	14 726
8. NORTH AFRICA and MIDDLE EAST	195 108	262 564	341 982
Algeria	18 919	26 946	37 041
Bahrain	313	410	515
Egyptian Arab Republic	41 963	52 709	64 421
Iran	38 126	51 033	64 916
Iraq	13 072	18 136	24 198
Jordan	3 244	4 657	6 510
Kuwait	1 353	2 101	2 936
Lebanon	2 658	3 301	3 992
Libyan Arab Jamahiriya	2 978	4 337	6 077
Morocco	20 296	27 840	36 509

(continued)

Annual mid-year population, medium variant 1980, 1990 and 2000[a/] by UNITAD regions (continued 3)

Region	Population in thousands 1980	1990	2000
8. NORTH AFRICA and MIDDLE EAST (continued)			
Oman	891	1 218	1 651
Qatar	237	330	425
Saudi Arabia	8 960	12 908	17 804
Sudan	18 371	24 491	32 328
Syrian Arab Republic	8 977	13 227	18 677
Tunisia	6 354	7 989	9 556
United Arab Emirates	726	1 025	1 286
Yemen	5 812	7 447	9 828
Democratic Yemen	1 858	2 459	3 312
9. SOUTH ASIA	941 151	1 153 436	1 376 194
Afghanistan	15 940	20 618	26 528
Bangladesh	88 164	116 164	148 361
Bhutan	1 296	1 628	2 030
Burma	35 289	44 738	55 108
India	684 460	820 860	960 611
Nepal	14 288	17 986	22 493
Pakistan	86 899	113 376	139 987
Sri Lanka	14 815	18 066	21 076
10. SOUTH EAST ASIA	308 110	370 773	432 323
Fiji	630	736	817
Hong Kong	5 106	6 250	6 973
Indonesia	148 033	173 530	198 687
Republic of Korea	38 455	45 022	50 786
Malaysia	14 068	17 689	21 269
Papua New Guinea	3 154	4 113	5 179
Philippines	49 211	62 830	77 036
Singapore	2 390	2 713	2 967
Taiwan	n.a.	n.a.	n.a.
Thailand	47 063	57 890	68 609
11. CPE, ASIA	1 078 682	1 231 858	1 382 472
China	994 913	1 127 636	1 257 298
Democratic Kampuchea	6 747	8 713	10 609
Dem. People's Rep. Korea	17 892	22 443	27 256
Lao People's Dem. Rep.	3 721	4 682	5 729
Mongolia	1 669	2 170	2 686
Viet Nam	53 740	66 214	78 894
UNITAD WORLD POPULATION (in 1 000)	4 422 113	5 229 437	6 101 140
TOTAL WORLD POPULATION (in 1 000)	4 432 147	5 241 911	6 115 514

Annex 4

Number of births, medium variant 1980, 1990 and 2000 a/

by UNITAD regions

Region	Births in thousands 1980	1990	2000
1. NORTH AMERICA	3 947	4 453	4 219
Canada	382	424	421
United States of America	3 565	4 029	3 798
2. WESTERN EUROPE	6 530	6 813	6 692
Austria	86	92	85
Belgium	121	122	117
Cyprus	12	12	10
Denmark	64	62	63
Finland	65	61	56
France	731	733	712
Germany, Fed. Rep. of	603	669	641
Greece	144	155	155
Iceland	4	4	4
Ireland	69	73	76
Israel	99	104	109
Italy	752	735	694
Luxemburg	4	4	3
Malta	6	6	5
Netherland	173	184	187
Norway	52	55	56
Portugal	175	176	167
Spain	654	657	668
Sweden	95	84	91
Switzerland	74	71	69
Turkey	1 489	1 704	1 702
United Kingdom	672	693	679
Yugoslavia	386	357	343
3. CPE EUROPE	6 714	6 996	6 799
Albania	78	79	72
Bulgaria	144	136	137
Czechoslovakia	275	242	255
German Democratic Rep.	221	216	190
Hungary	170	139	139
Poland	670	633	595
Romania	410	395	411
USSR	4 746	5 156	5 000
4. JAPAN	1 722	1 486	1 749

(continued)

a/ Demographic Indicators of Countries: Estimates and projections as assessed in 1980, United Nations ST/ESA/SER.A/82, New York, 1982

Number of births, medium variant 1980, 1990 and 2000 a/

by UNITAD regions (continued 1)

Region	Births in thousands 1980	1990	2000
5. OTHER DEVELOPED	1 329	1 647	1 938
South Africa	1 038	1 342	1 612
Australia	234	243	263
New Zealand	57	62	63
6. LATIN AMERICA	11 406	13 194	14 470
Argentina	557	583	589
Bahamas	n.a.	n.a.	n.a.
Barbados	6	5	5
Bolivia	235	293	359
Brazil	3 837	4 335	4 810
Chile	271	295	290
Colombia	785	885	887
Costa Rica	61	71	77
Cuba	162	187	195
Dominican Republic	205	226	248
Equator	310	395	457
El Salvador	183	228	278
Guatemala	278	327	401
Guyana	26	25	23
Haiti	229	288	361
Honduras	160	187	246
Jamaica	59	59	54
Martinique	6	6	6
Mexico	2 484	2 887	2 995
Nicaragua	118	148	182
Panama	56	60	64
Paraguay	108	136	151
Peru	637	818	989
Surinam	14	21	21
Trinidad and Tobago	25	26	24
Uruguay	59	61	63
Venezuela	530	642	695
7. AFRICA (South Sahara)	14 783	19 475	24 236
Angola	317	408	508
Benin	160	217	280
Botswana	38	52	68
Burundi	182	237	283
Central African Republic	96	125	155
Chad	187	234	276
Comoros	16	19	22
Congo	64	83	105
Ethiopia	1 499	1 865	2 231
Equatorial Guinea	15	18	23

(continued)

Number of births, medium variant 1980, 1990 and 2000 [a/]

by UNITAD regions (continued 2)

Region	Births in thousands 1980	1990	2000
7. AFRICA (South Sahara)(continued)			
Gabon	17	21	23
Gambia	27	35	43
Ghana	525	698	871
Guinea	217	280	349
Guinea Bissau	22	26	31
Ivory Coast	351	457	566
Kenya	806	1 173	1 619
Lesotho	50	63	73
Liberia	88	122	158
Madagascar	369	467	557
Malawi	291	390	490
Mali	321	425	538
Mauritania	77	103	130
Mauritius	25	25	22
Mozambique	441	577	729
Namibia	41	53	65
Niger	255	348	444
Nigeria	3 552	4 763	5 977
Reunion	12	12	12
Rwanda	221	302	394
Senegal	254	323	381
Sierra Leone	148	189	226
Somalia	179	257	277
Swaziland	25	32	39
Togo	118	154	187
Uganda	549	749	978
United Rep. of Cameroon	338	417	488
United Rep. of Tanzania	772	1 030	1 291
Upper Volta	310	394	465
Zambia	263	355	452
Zaire	1 222	1 536	1 848
Zimbabwe	323	441	562
8. NORTH AFRICA and MIDDLE EAST	7 924	9 657	10 798
Algeria	828	1 140	1 306
Bahrain	10	12	13
Egyptian Arab Republic	1 515	1 599	1 718
Iran	1 574	1 810	1 858
Iraq	567	700	803
Jordan	140	188	230
Kuwait	51	73	87
Lebanon	82	91	92
Libyan Arab Jamahiriya	128	177	226

(continued)

Number of births, medium variant 1980, 1990 and 2000 a/

by UNITAD regions (continued 3)

Region	Births in thousands 1980	1990	2000
8. NORTH AFRICA and MIDDLE EAST			
Morocco	853	1 056	1 143
Oman	41	52	63
Qatar	6	10	13
Saudi Arabia	372	505	643
Sudan	787	993	1 166
Syrian Arab Republic	381	546	652
Tunisia	216	236	218
United Arab Emirates	19	27	36
Yemen	270	334	400
Democratic Yemen	84	108	131
9. SOUTH ASIA	33 387	35 369	35 851
Afghanistan	728	905	1 019
Bangladesh	3 859	4 615	4 886
Bhutan	52	62	67
Burma	1 285	1 454	1 518
India	22 982	23 241	23 271
Nepal	590	684	748
Pakistan	3 498	3 964	3 933
Sri Lanka	393	444	409
10. SOUTH EAST ASIA	9 512	9 802	9 466
Fiji	17	18	16
Hong Kong	88	112	97
Indonesia	4 764	4 763	4 511
Republic of Korea	934	959	896
Malaysia	438	478	460
Papua New Guinea	126	145	150
Philippines	1 668	1 797	1 846
Singapore	40	47	41
Taiwan	n.a.	n.a.	n.a.
Thailand	1 437	1 483	1 449
11. CPE, ASIA	23 533	23 966	24 366
China	20 518	20 846	21 214
Democratic Kampuchea	214	331	312
Dem. People's Rep. Korea	548	616	638
Lao People's Dem. Rep.	155	171	174
Mongolia	58	65	64
Viet Nam	2 04	1 937	1 962
UNITAD TOTAL	120 787	132 858	140 584
WORLD TOTAL	121 067	133 182	140 905

Annex 5

Technical data of bulk DPT vaccine production in fermenters and in shaken/static cultures

WHO Name: Diphtheria-pertussis-tetanus vaccine

Other Common Name: DPT vaccine

Single Human Dose: 0.5 ml of DPT vaccine containing:

15 Lf	diphtheria toxoid
5 Lf	tetanus toxoid
15×10^9	Bordetella pertussis bacilli (killed)[a/]

Parameters of the Studied Process[b/]

(a) Diphtheria component

Fermenter size	50 litres
Operating volume	30 litres
Operating volume/fermenter size	60%
Toxin concentration at harvest	100 Lf/ml
Cultivation cycle	48 hours
Number of cultivations/year	34
Quantity of diphtheria toxoid produced in a single cultivation	3×10^6 Lf
Recovery efficiency	70%
Quantity of diphtheria toxoid produced from a single harvest	2.1×10^6 Lf
Production cycle, of which	125 days
Quality control	84 days

(b) Tetanus toxoid component

Fermenter size	50 litres
Operating volume	30 litres
Operating volume/fermenter size	60%
Toxin concentration at harvest	30 Lf/ml
Cultivation cycle	168 hours

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a/ The WHO requirement is not less than 30, 40 and 4 IU, respectively.

b/ Data received from a European manufacturer.

Number of cultivations/year	38
Quantity of tetanus toxoid produced in a single cultivation	$9x10^5$Lf
Recovery efficiency	70%
Quantity of tetanus toxoid produced from a single harvest	$6.3x10^5$Lf
Production cycle, of which	49 days
Quality control	28 days

(c) Pertussis vaccine component

Fermenter size	50 litres
Operating volume	30 litres
Operating volume/fermenter size	60%
Bacterium count at harvest	$3x10^{10}$ bacilli/ml
Cultivation cycle	48 hours
Number of cultivations/year	112
Quantity of pertussis vaccine produced in a single fermentation	$9x10^{14}$ bacilli
Recovery efficiency	70%
Quality of pertussis vaccine produced from a single harvest	$6.3x10^{14}$ bacilli
Production cycle, of which	41 days
Quality control	28 days

(d)	Adsorption and blending of the 3 components	2 days
	Quality control	42 days
	Total lead time of final bulk DPT vaccine production	169 days

Parameters of the process in static or shaken cultures

(a) Diphtheria component

No. of 2-l Roux bottles	200
Operating volume	100 litres
Toxin concentration at harvest	30 Lf/ml
Cultivation cycle, static	7 days
Yield from one pool of cultivation	$3x10^6$ Lf
Recovery efficiency	70%

Batch yield	3.5×10^6 Lf
Production cycle, of which	130 days
Quality control	84 days

(b) Tetanus toxoid component

No. of 15-l glass bottles	20
Operating volume	200 litres
Toxin concentration at harvest	20Lf/ml
Cultivation cycle, static	7 days
Yield from one pool of cultivation	4×10^6 Lf
Recovery efficiency	70%
Batch yield	2.8×10^6 Lf
Production cycle, of which	49 days
Quality control	28 days

(c) Pertussis vaccine component

No. of 1-l flasks	50
Operating volume	20 litres
Bacterium count at harvest	2.5×10^{10} bacilli/ml
Cultivation cycle, shaken	2 days
Yield from one pool of cultivation	5×10^{14} bacilli
Recovery efficiency	70%
Batch yield	3.5×10^{14} bacilli
Production cycle, of which	41 days
Quality control	28 days

Annex 6

Directory of Sources of Technology for the Production of Immunizing Agents

1. B.C.G. Vaccine Laboratory,
(Directorate General of Health Services)
Ministry of Health
Government of India
Guindy
MADRAS-32
India

Cables: CALMETTE
Telex: - -
Telephone: 432976, 431745

2. Behringwerke Aktiengesellschaft
Postfach 1140
D-3550 MARBURG 1
GFR

Cables: BEHRINGWERKE MARBURGLAHN
Telex: 04-82-320
Telephone: (0-64-21)-30-21

3. Bureau of Research and Laboratories
Ministry of Health
Republic of the Philippines
P.O. Box 911
MANILA
Republic of the Philippines

Cables: -
Telex: -
Telephone: 21-94-39, 44-10-92

4. Commonwealth Serum Laboratories
45 Poplar Road
Parkville
VICTORIA, 3052
Australia

Cables: SERUMS MELBOURNE
Telex: AA 32789
Telephone: 389-1911

5. Connaught Laboratories Limited
1755 Steeles Avenue West
WILLOWDALE, M2N 5T8, Ontario
Canada

Cables: CONTOX TORONTO
Telex: 06 22184
Telephone: (416) 667-2701

6. Department of Public Health
State of Michigan
3500 N. Logan, P.O. Box 30035
LANSING,
Michigan 48909
USA

Cables: -
Telex: -
Telephone: -

7a. Glaxo Holdings p.l.c.
Clarges House 6-12 Clarges Street
LONDON W1Y 8DH
England

Cables: GLAXOGROUP LONDON W1
Telex: 25456
Telephone: 01-493 4060

7b. Glaxo Laboratories (India) Limited,
Dr. Annie Besant Road, Worli
BOMBAY 40 00 25
India

Cables:
Telex:
Telephone:

8. HUMAN Institute for
Serobacteriological Research
and Production, represented by
MEDIMPEX (Hungarian Trading Company for
Pharmaceutical Products
P.O. Box 126
H-1808 BUDAPEST 5
Hungary

Cables: MEDIMPEX, BUDAPEST
Telex: (861) 225477
Telephone: 183 - 955

9. Institut Armand-Frappier
527 boulevard des Prairies,
P.O. Box 310
Laval-des-Rapides
LAVAL, Quebec H7N 423
Canada

Cables: INSTFRAP-VDL
Telex: 05-25859
Telephone: (514) 687-5010

10. Institute of Immunology-Zagreb
Rockefellerova 2
41000 ZAGREB
Yugoslavia

Cables: SERUMVAKCINA
Telex: 21864 VACC YU
Telephone: 277-044, 271-055

11. Institute for Medical Research
Jalan Pahang
KUALA LUMPUR 02-14
Malaysia

Cables: RESEARCH
Telex:
Telephone: 03-986033

12. Institut Mérieux
17, rue Bourgelat
LYON 69223
France

Cables:
Telex: 310627 Mérieux Lyon
Telephone: (78) 38-06-10

13. Institut Pasteur d'Algérie
Ministère de la Santé
République d'Algérie
ALGER
Algérie

Cables:
Telex: 53.715
Telephone: 65-34-96/98,
65-88-60/62

14. National Institute of Hygiene
represented by
MEDIMPEX (Hungarian Trading Company for
Pharmaceutical Products)
P.O. Box 126
H-1808 BUDAPEST 5
Hungary

Cables: MEDIMPEX, BUDAPEST
Telex: (861) 225477
Telephone: 183 - 955

15. National Public Health Institute
Mannerheimintie 166
SF-00280 HELSINKI 28
Finland

Cables:
Telex:
Telephone: 358-0-47441

16. Pasteur Institute of India
Coonoor 643 103
NILGIRIS
India

Cables:
Telex:
Telephone:

17. Refik Saydam
Central Institute of Hygiene
ANKARA
Turkey

Cables: RESAMENS Ankara
Telex:
Telephone:

18. The Thai Red Cross Society,
Queen Saovabha Memorial Institute
Rama IV Street
BANGKOK, 5
Thailand 10500

Cables:
Telex:
Telephone:

19. Vaccine Institute
Government of Karnataka
BELGAUM-590 006
Karnataka State
India

Cables: 'VACCINE'
Telex:
Telephone: 20052

20. Akademie der Wissenschaften der DDR,
Zentralinstitut für Mikrobiologie und
Experimentelle Therapie,
Beutenbergstrasse 11
DDR - 6900 JENA

Cables: ZIMET JENA
Telex: 5886142 zimt dd
Telephone: 88 50

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Some aspects of the Production of Immunizing Agents in Developing Countries

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